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VIOFORM for use in LEUKORRHEA caused by trichomonas vaginalis

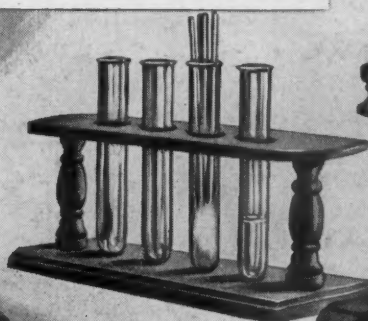
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Original Communications

SOME OBSERVATIONS ON THE HORMONAL CONTENT OF OVARIAN CYSTS ASSOCIATED WITH PREGNANCY*

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the Chicago Lying-in Hospital)*

THIS report is a part of a general study^{1, 2} of the relationship of hormones to ovarian tumors and is an attempt to correlate the occurrence of hormones in the cyst fluid with the histology of the tumor. A previous report² was concerned with the occurrence of estrogen in the cyst fluids of benign and malignant ovarian tumors from nonpregnant patients. Because of certain hormonal implications the cysts associated with pregnancy were omitted from that study and are the subject of this report.

There are few references in the literature to the occurrence of hormones in ovarian cysts associated with pregnancy. (Table I.) The presence of estrogen was reported by Allen, Pratt, Newell and Bland³ Philipp⁴ and Geller⁵ but it was not found by Moulonguet⁶ and Lepper, Pratt, Pratt and Vaux.⁷ Gonadotropin was found by Zondek,⁸ Philipp,⁴ Geller⁵ and Lepper et al.⁷ In corpus luteum cysts associated with hydatidiform mole and chorionepithelioma, Siegmund,⁹⁻¹¹ von Probstner¹² and Zondek¹³ found both estrogen and gonadotropin; Ruzieska,¹⁴ McLaughlin¹⁵ and de Alvarez¹⁶ reported the presence of gonadotropin and Allen¹⁷ the presence of estrogen. The hormonal content of human corpora lutea of pregnancy has been investigated by Allen, Pratt and Doisy,¹⁸ Gillman and Smyth^{19, 20} and Gluckman.²¹

*This work has been supported by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

TABLE I. HORMONAL CONTENT OF CYST FLUIDS

INVESTIGATOR	TYPE OF CYST	PERIOD OF PREGNANCY	AMOUNT OF FLUID IN CYST (C.C.)	GONADOTROPIN	ESTROGEN
OVARIAN CYSTS ASSOCIATED WITH PREGNANCY					
Moulouguet (1928)	Corpus luteum	Post partum	0.5		Negative in rats
Allen, Pratt, Newell and Bland (1930)	Corpus luteum	2 to 3 mo.	17.5		
Zondek (1931)	Pseudomucinous	8 wk.	500	1 M.U. per c.c.	0.5 c.c. positive in rats
		6 wk.	65	80 M.U. Prolan A; 130 M.U. Prolan B	
Philipp (1934)	Pseudomucinous	2 to 4 mo.		2.6 c.c. positive in mice	3 c.c. positive in mice
	Serous	2 to 4 mo.		2.6 c.c. positive in mice	3 c.c. positive in mice
	Corpus luteum	2 to 4 mo.		2.6 c.c. positive in mice	3 c.c. positive in mice
	Corpus luteum	2 to 4 mo.		2.6 c.c. positive in mice	3 c.c. positive in mice
Geller (1934)	Serous	4 mo.	17 L	Positive in mice	Positive in mice
Lepper, Pratt, Pratt, and Vaux (1938)	Pseudomucinous	23 wk.		48 c.c. positive in rabbit	8 to 12 c.c. neg. in rats
	Lutein	12 wk.		48 c.c. positive in rabbit	8 to 12 c.c. neg. in rats
	Germinal	18 wk.		20 c.c. sl. positive Prolan A and neg. Prolan B in rabbit	8 to 12 c.c. neg. in rats
OVARIAN CYSTS ASSOCIATED WITH HYDATIDIFORM MOLE AND CHORIONEPITHELIOMA					
Siegmund (1931)	Corpus luteum			500,000 M.U. per L	10,000 M.U. per L
Siegmund (1932)	Corpus luteum			1.2 to 2.4 c.c.; strongly positive Prolan A; weakly positive Prolan B	>10,000 M.U. per L
				>200,000 M.U. per L	>2,000 M.U. per L
				1,000 M.U. per L	>2,000 M.U. per L
				<20,000 M.U. per L	
Siegmund (1934)	Corpus luteum			Positive	Small amount
	Corpus luteum			Prolan B strongly positive	
von Probstner (1935)	Corpus luteum (bilateral)			5,000 M.U. per L	26 c.c. positive in rats
Ruzicka (1935)	Corpus luteum			260 (total)	
Allen (1940)	Corpus luteum (bilateral)			Large amount	
McLaughlin (1941)	Corpus luteum (bilateral)			Strongly positive	
de Alvarez (1942)	Corpus luteum			5,500 M.U. Prolan A; 550 M.U. Prolan B per L	2,000 M.U. per L
Zondek (1942)	Corpus luteum				
PAROVARIAN CYSTS ASSOCIATED WITH PREGNANCY					
Zondek (1931)	Parovarian	8 wk.	145	Negative	
Kittner (1933)	Parovarian	8 wk.	140	1.2 to 2.4 c.c. positive in mice	
Philipp (1934)	Parovarian	2 to 4 mo.	550	2.6 c.c. Prolan positive in mice	3 c.c. positive in mice
Pardini (1941)	Parovarian		8	6 c.c. negative in rabbit	
	Parovarian		2500	6 c.c. negative in rabbit	
	Parovarian		30	6 c.c. negative in rabbit	

Philipp⁴ reported the presence of both estrogen and gonadotropin in the fluid of a parovarian cyst associated with pregnancy; gonadotropin was found by Kittner²² but not by Zondek⁸ and Pardini.²³

We have investigated the estrogen content of the cyst fluids from 30 ovarian cysts, 3 parovarian cysts and 2 other genital cysts associated with pregnancy. The gonadotropin content was studied in a few of these. Gonadotropin was generally present but estrogen was not always found. This may be due to a failure of the hormone to be stored in the cyst fluid or to the fact that the tumors were usually removed early in pregnancy when the estrogen level is comparatively low.

Methods

The ovarian tumors were received directly from the operating room and described. The fluid was aspirated from each cyst cavity and a specimen of tissue removed from the wall of each cavity for histologic examination. In multilocular tumors the different locules are designated by letters; e.g., cyst No. 277 had 3 cyst cavities, namely, A, B and C. Because of the small amounts of material available for study strictly quantitative assay of the hormonal content could not be made; therefore, the values are expressed in rat units based on the smallest amount of material which gave a positive response or the largest amount tested which gave a negative response.

Estrogen.—When fluids were tested without extraction the fluid was injected subcutaneously into ovariectomized adult albino rats, in three doses during an eight-hour period, and the vaginal smears read at 48 and 56 hours. When it was possible or desirable to test large amounts of fluid, extracts were made according to a method² previously described and involving alcohol precipitation, evaporation in vacuo, acidification and extraction with ether. Extracts were made up in olive oil and administered subcutaneously in one dose. Fluids were not tested at higher levels than 200 c.c. per dose. Wherever possible, at least three extracts were made.

Gonadotropin.—Fluids were tested for gonadotropin in 21-day-old male or female rats. The fluid was injected subcutaneously twice daily for three days, the animals were sacrificed at 96 hours, and either the weight response of the seminal vesicle or the blood point response in the ovary was used as the criterion of a positive response.

Histology.—The tissues were fixed in formalin and stained with hematoxylin and eosin.

Clinical Material

In the present study there are 30 cases of ovarian cysts associated with pregnancy; in 23 cases (76.7 per cent) the cysts were removed during pregnancy and in seven cases, during the post-partum period. The 16 cases mentioned briefly in our first report are included in this series. In a previous paper² we reported hormonal studies of the cyst

fluids of 189 cases of benign ovarian cysts not associated with pregnancy. For purposes of comparison a group of these patients has been used as a control group in this report. This group consists of 114 patients with single type ovarian tumors (only one type of cyst present) and excludes patients with multiple type tumors (more than one type of cyst present), bilateral tumors and those which are the second occurrence of an ovarian tumor in the same patient.

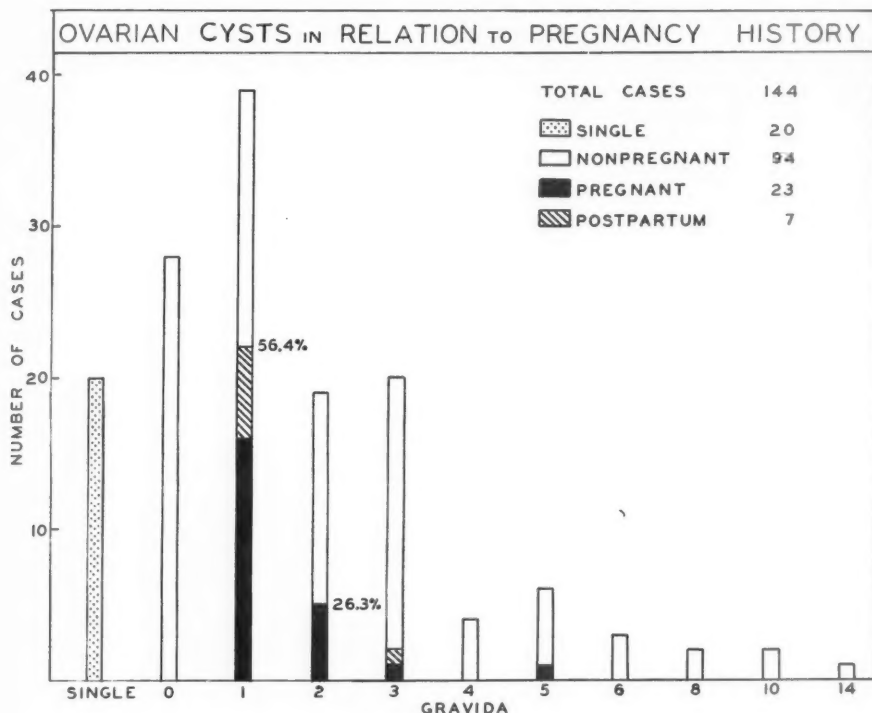


Fig. 1.

Classification of Ovarian Cysts

All of the ovarian cysts were benign. They were classified as follicle and corpus luteum cysts (pseudoneoplasms), simple serous, papillary serous, pseudomucinous and dermoid cysts.

Pregnancy History

In the total group of 144 ovarian cysts upon which hormonal studies have been made, 114 were in nonpregnant patients (previously reported²) and 30 were associated with pregnancy. In the entire group, 33.3 per cent (48 cases) were found among single women (20 cases) and married women (28 cases) with no history of pregnancy; 66.7 per cent (96 cases) were among patients with a history of 1 or more pregnancies. About one-fifth of the cases (30 cases) was associated with a pregnancy; in 23 cases (16 per cent) the cysts were removed during pregnancy and in seven cases (4.9 per cent) in the post-partum period. In

the group of 96 cases with histories of one or more pregnancies, 39 patients (40.6 per cent of the group or 27.1 per cent of the entire series) gave a history of one pregnancy; the cysts were associated with the pregnancy in 56.4 per cent of the cases (22 cases) and there was no relation to a pregnancy in 43.6 per cent (17 cases). Of the 22 cysts associated with the first pregnancy, 16 were removed during pregnancy and six in the post-partum period; 73.3 per cent of the cysts (22 of 30) associated with pregnancy were in primiparous patients. Of the entire series, 13.2 per cent (19 cases) gave histories of two pregnancies; in 26.3 per cent of these (5 cases) the cysts were removed during pregnancy, and 73.7 per cent (14 cysts) were not associated with the pregnancy. In two cases cysts were associated with the third pregnancy and in one with the fifth pregnancy. (Fig. 1.)

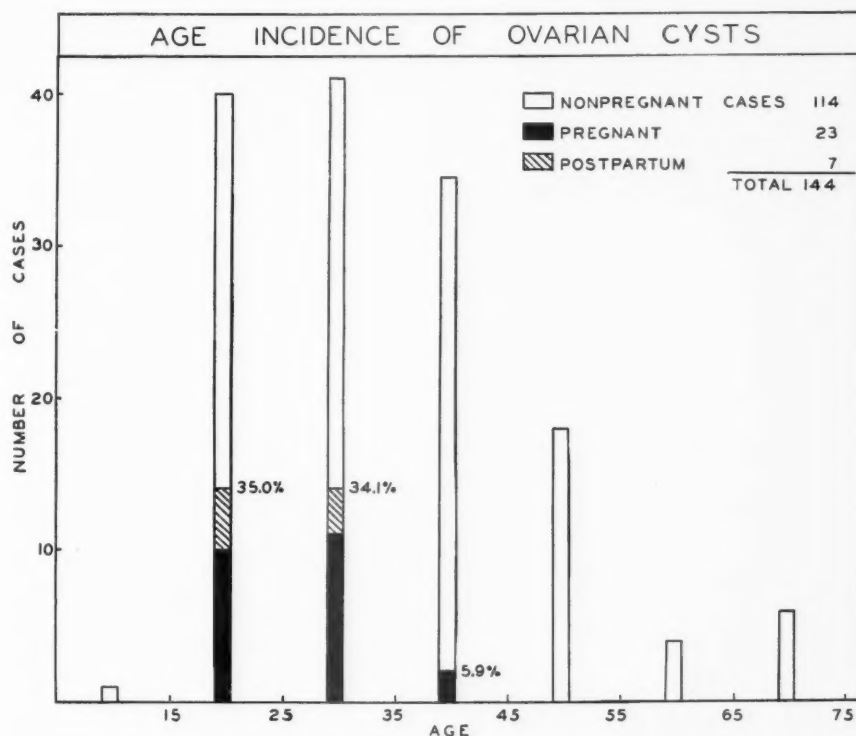


Fig. 2.

Age Incidence

In the same group of 144 cases of ovarian cysts, 114 cases were among nonpregnant patients and 30 cases were associated with pregnancy. The ages at which these cysts occurred are shown by decades 15 to 24, 25 to 34, etc., in Fig. 2. In this series 79.9 per cent (115 cases) occurred in the three decades, 15 to 44 years, and the distribution was approximately the same in each of these decades, 27.8 per cent, 28.5 per cent and 23.6 per cent, respectively. The two decades, 15 to 24 and 25 to 34

years, include 56.3 per cent (81 cases) of all the cases and 93.3 per cent (28 cases) of the cysts associated with pregnancy. There were 14 cases associated with pregnancy in each of these decades or 35.0 per cent and 34.1 per cent, respectively, of the cysts occurring in those decades.

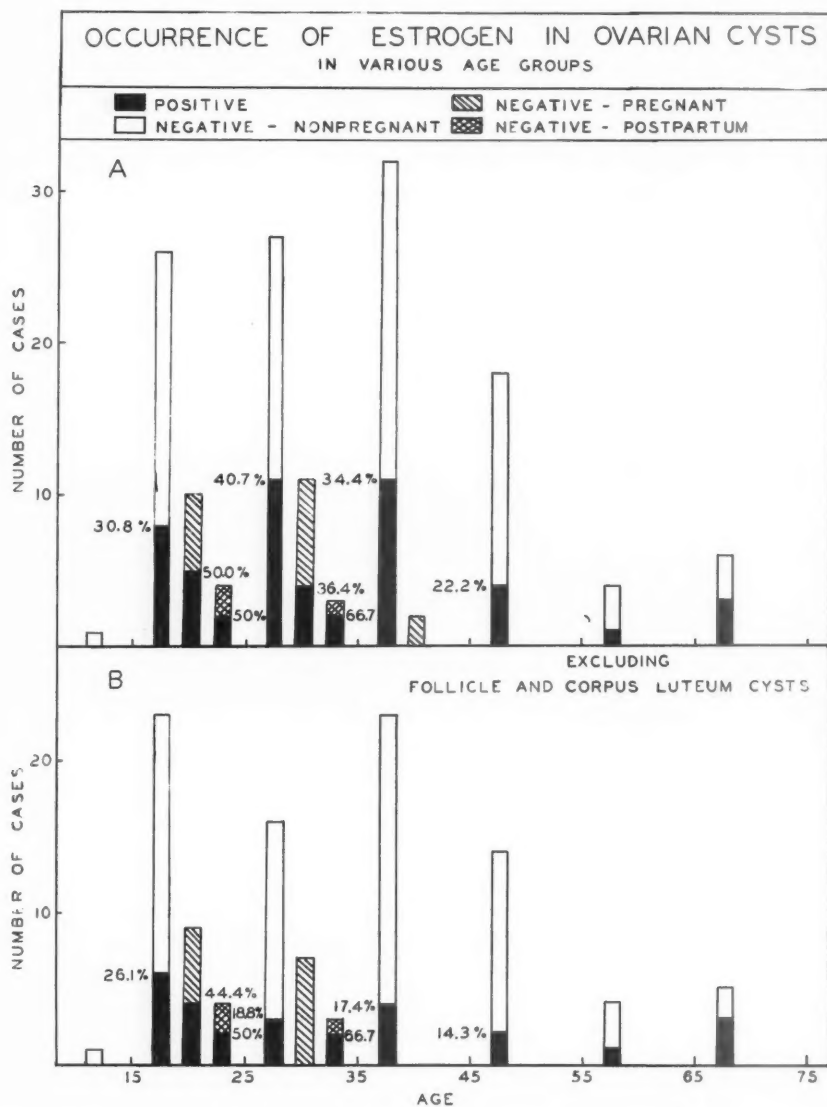


Fig. 3.

Occurrence of Estrogen in Ovarian Cysts in Various Age Groups

Occurrence of estrogen in ovarian cysts in various age groups is shown in Fig. 3A. In the decade 15 to 24 years, 30.8 per cent (8 of 26 cysts) in the nonpregnant patients, 50 per cent (5 of 10 cysts) in the pregnant patients and 50 per cent (2 of 4 cysts) removed from patients in the post-partum period contained estrogen. In the following decade, 25

to 34 years, 40.7 per cent (11 of 27 cysts) from nonpregnant patients, 36.4 per cent (4 of 11 cysts) from pregnant patients and two of three cysts removed post partum showed estrogen.

Since follicle and corpus luteum cysts are expected to contain estrogen, cysts of these types were excluded from the data appearing in Fig. 3B. There were no follicle cysts in the pregnancy group. These data include 86 cases from the series of nonpregnant patients and 23 cases in which the cysts were associated with pregnancy. In the decade, 15 to 24 years, 26.1 per cent (6 of 23) of the cysts in nonpregnant patients, 44.4 per cent (4 of 9) of the cysts removed during pregnancy,

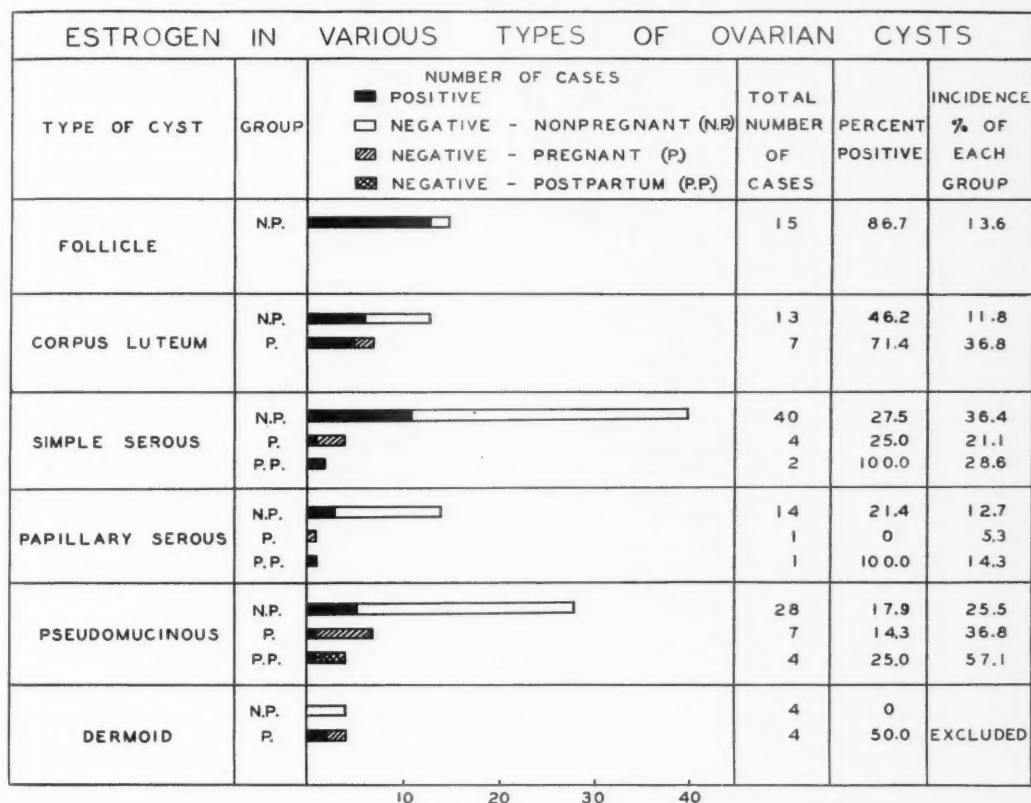


Fig. 4.

and 50 per cent (2 of 4) removed post partum contain estrogen. In the decade, 25 to 34 years, 18.8 per cent (3 of 16) of the cysts in nonpregnant patients, none in pregnant patients and 66.7 per cent (2 of 3) of the cysts removed post partum contained estrogen.

Incidence of Various Types of Cysts

The incidence of the various types of ovarian cysts is shown in Fig. 4. Because of the nature of dermoid cysts and the type of cyst contents not all dermoids were tested for hormone. Consequently, they are excluded in determining the incidence of the series. In the group of 110

cysts removed from nonpregnant patients the incidence was: follicle, 15 (13.6 per cent); corpus luteum, 13 (11.8 per cent); simple serous, 40 (36.4 per cent); papillary serous, 14 (12.7 per cent); pseudomucinous, 28 (25.5 per cent). In the group (19) removed during pregnancy the incidence was: follicle, none; corpus luteum, 7 (36.8 per cent); simple serous 4 (21.1 per cent) papillary serous 1 (5.3 per cent); pseudomucinous 7 (36.8 per cent). In the group of 7 cysts removed in the post-partum period the incidence was: follicles, none; corpus luteum, none; simple serous, 2 (28.6 per cent); papillary serous, 1 (14.3 per cent); pseudomucinous, 4 (57.1 per cent). Considering the entire group of 26 cysts (excluding dermoids) associated with pregnancy, the incidence of corpus luteum cysts (26.9 per cent) and of pseudomucinous cysts (42.3 per cent) seems higher than in the nonpregnant group and that of simple serous (23.1 per cent) and of papillary serous (7.7 per cent) seems somewhat lower. However, the series is too small to draw definite conclusions.

Occurrence of Estrogen in Ovarian Cyst Fluids

For the various types of cyst fluids in the group of 114 single type cysts, previously reported,² the percentages of the cysts which contained estrogen were as follows: follicle, 86.7 per cent (13 of 15 cysts); corpus luteum, 46.2 per cent (6 of 13 cysts); simple serous, 27.5 per cent (11 of 40 cysts); papillary serous, 21.4 per cent (3 of 14 cysts); pseudomucinous, 17.9 per cent (5 of 28 cysts). In the group of 23 cysts removed during pregnancy the percentages of the various types which contained estrogen were: no follicle cysts; corpus luteum, 71.4 per cent (5 of 7 cysts); simple serous 25 per cent (1 of 4 cysts); papillary serous (one negative); pseudomucinous, 14.3 per cent (1 of 7 cysts); dermoid, 50 per cent (2 of 4 cysts). In the group of 7 cysts removed post partum there were no follicle or corpus luteum cysts; 2 simple serous cysts, one papillary serous cyst and one of four pseudomucinous cysts contained estrogen. In the entire group of cysts associated with pregnancy, the percentage of cysts containing estrogen was 43.3 per cent in contrast to 33.3 per cent of positive cysts in the nonpregnant patients. (Fig. 4.)

When the cysts commonly containing estrogen, namely, follicle and corpus luteum cysts, are excluded, 34.8 per cent of the cysts associated with pregnancy and 22.1 per cent of the cysts not associated with pregnancy contain estrogen. Estrogen was found in 25 per cent of the cysts (4 of the 16 cysts) removed during pregnancy and 57.1 per cent (4 of 7 cysts) removed post partum.

In general, the amount of estrogen found is about that reported previously.² In the corpus luteum cysts removed during pregnancy the amount of estrogen found ranged from 0.07 to 2.5 R.U. per c.c. and in cysts from nonpregnant patients previously reported ranged from 0.12 to 2 R.U. per c.c. This is probably less than the amount found by

Allen, et al.¹⁸ in the fluids of corpora lutea of nonpregnant patients or human corpora lutea of pregnancy. One simple serous cyst contained 0.33 R.U. per c.e.; in one pseudomucinous cyst, No. 210, one fluid showed 0.005 R.U. per c.e. and one, 0.01 R.U. per c.e., and two others showed less than 0.03 and 0.05 R.U. per c.e., respectively. Fluids from two dermoids were negative; from another the fluid showed 0.005 R.U. per c.e.; the two fluids from another dermoid cyst, No. 226, showed 0.02 R.U. per c.e. in one fluid and less than 0.06 R.U. per c.e. in the other.

The failure to find estrogen in all cysts during pregnancy may be due to the small amount of fluid available for testing or to the fact that many cysts were removed early in pregnancy when the estrogen level is comparatively low. Although more cysts from post-partum patients contain estrogen they do not contain unusual amounts of this hormone, and the tumor probably does not act as a hormonal depot. (Table II.)

Occurrence of Gonadotropin in Ovarian Cyst Fluids

Not all cyst fluids were tested for gonadotropin. Fluid from two pseudomucinous cysts, No. 28 and No. 64, each showed 0.25 R.U. per c.e., and the fluid of another pseudomucinous cyst, 210A, showed 0.67 R.U. per c.e. The tumors were removed during the twelfth, seventeenth, and twenty-eighth week of pregnancy, respectively. One simple serous cyst, No. 3, removed one week post partum, contained fluid showing 0.25 R.U. per c.e. Considering the amount of gonadotropin circulating in the body during pregnancy, it is not surprising to find it in the cyst fluid. However, the concentration is considerably lower than is found in blood serum in pregnancy. Thirteen cyst fluids from ovarian tumors occurring in nonpregnant patients were tested for gonadotropin but amounts varying from 1 to 18 c.e. were negative.

Miscellaneous

Fluid was removed from the corpus luteum in two cases (No. 44 and No. 115) in which pregnancy was interrupted because of cardiac disease. These were not included in the general series because no tissue was obtained for histologic control. One fluid contained less than 1.11 R.U. per c.e. of estrogen and the other 0.33 R.U. per c.e.

A case with a placental polyp was studied. Because of a suspicion of malignancy, hysterectomy and bilateral oophorectomy were performed. Both ovaries contained cystic follicles; the right ovary, No. 135, contained 5 c.e. and the left, No. 136, 5.4 c.e. (composite specimen). Fluid from the right ovary contained 5 R.U. per c.e. of estrogen and less than 0.83 R.U. per c.e. of gonadotropin; the left ovary showed less than 1.67 R.U. per c.e. of estrogen and 5 R.U. per c.e. of gonadotropin. There was little epithelial lining on the wall of the follicles in the left ovary, showing no estrogen. The endometrium showed actively growing chorionic tissue.

TABLE II. HORMONAL CONTENT OF CYSTS ASSOCIATED WITH PREGNANCY

TYPE OF CYST	CYST NO.	AMOUNT OF CYST FLUID C.C.	ESTROGEN		GONADO- TROPIN		R.U. PER C.C.	CLINICAL OBSERVATIONS				REMARKS		
			+	-	+	-		AGE	GRAV.	PREG.	WK.		DELIVERY WK.	TYPE
OVARIAN CYSTS REMOVED DURING PREGNANCY														
Corpus luteum (7)	23	96.5	3			0.33		33	1	7			Laparotomy	
	65	20.5	0.4			2.50		25	2	3			Laparotomy	
	114	60			50	<0.02		39	1	36	36		Twisted pedicle, necrotic, gangrenous	
	122	1.5			1	<1.00		35	2	11	40		Diabetes	
	223	92	15			0.07		30	1	16	35		Pre-eclampsia	
	277 A	189.5	3			0.33		23	1	10	41		Progesterin for 2 weeks, postoperative	
	B	51	5				0.20							
	C	2.4			1.5	<0.67								
	280	35	3			0.33		33	5	10			Progesterin for 2 days, postoperative	
Simple serous (4)	120	135			45	<0.02		28	1	18	40		Natural	
	212	174	3			0.33		23	1	8				
	265	310			200	<0.005		29	1	13	40		Forceps	
	287 A	180			115	<0.009		26	1	15	39		Forceps	
	B	34			26	<0.04								
	228	31			10	<0.10		29	1	22	38		Natural	
Papillary serous (1)														
Pseudomucinous (7)	28	600			100	<0.01	4	28	1	12	40		Natural	
	64	380			100	<0.01	4	25	1	17	39		Natural	
	148	160			145	<0.007		19	1	17	40		Natural	
	167	400			200	<0.005		23	3	20	40		Natural	
	210 A	>6135	200			0.005	1.5	0.67	23	1	28	40	Natural	
	B	25			20	<0.05								
	C	38			32	<0.03								
	D	97	80			0.01								
	283 A	4025			200	<0.005		23	1	13	40		Forceps	
	B	34			30	<0.03								
	C	17			15	<0.07								
294 A	81			67.5	<0.02			33	2	39	39		Ces. sect.	
	B	35			31.3	<0.03								

Tuberculosis

Dermoid (4)	34	2150	112	<0.009	22	1	10	Missed ab.
	95	428	200	0.005	21	1	11	Forceps
	169	594	200	<0.005	30	2	11	Natural
	226 A	6780	50	0.02	21	2	17	38
B	38		17	<0.06				
OVARIAN CYSTS REMOVED POST PARTUM								
Simple serous (2)	3	3050	4	0.25	26	1	1 PP	Forceps
	250	4026	25	0.04	23	3	2 1/2 PP	Natural
Papillary serous (1)	211	1065	125	0.008	24	1	9 PP	Natural
Pseudomucinous (4)	38	3810	150	<0.007	28	1	5 PP	Induced
	73	416	150	<0.007	23	1	8 PP	Natural
	144	850	200	<0.005	21	1	13 PP	Forceps
	291	2280	200	0.005	28	1	5 PP	Severe pre-eclampsia Delivered elsewhere Twisted; tumor for 8 years
MISCELLANEOUS								
Corpus luteum	44	2.2	0.9	<1.11	42	3	9	Cardiac; laparotomy
Corpus luteum	115	18	3	0.33	27	1	13	Cardiac; laparotomy
Follicle	135	5	0.2	5	1.2	3	4	Placental polyp; bilateral cysts
Follicle	136	5.4	0.6	<1.67	5			
NONOVARIAN CYSTS REMOVED DURING PREGNANCY								
Parovarian	17	56	15	0.06	30	1	39	Twisted pedicle
Parovarian	102	178	25	<0.04	32	5	4° PP Term	Ruptured uterus
Parovarian	255	48	32	<0.03	28	3	10	Meningo-encephalitis 2 years before
Gartner's duct	F2	13.5	13	<0.08	22	2	30	Natural
Cystic fibroid	F9	51	15	0.06	41	1	39	Porro C.S.

Of the seven corpus luteum cysts two were associated with ectopic pregnancies, one patient aborted, one was delivered by cesarean section, one by forceps and two delivered naturally. In 16 patients with other types of cysts removed during pregnancy, there was one case of missed abortion, four cases of delivery by forceps, one case with cesarean section, nine cases with natural delivery and one case was not followed.

Nonovarian Cysts

Fluids from three parovarian cysts associated with pregnancy were tested for estrogen; one cyst, No. 17, contained 0.06 R.U. per c.c. and two others, No. 102 and No. 255, contained less than 0.04 and 0.03 R.U. per c.c., respectively. Parovarian cyst No. 17 contained less than 0.13 R.U. per c.c. of gonadotropin. Fluid from a cyst of Gartner's duct contained less than 0.08 R.U. per c.c. of estrogen. Fluid from a cystic fibroid contained 0.06 R.U. per c.c. of estrogen and 10 R.U. per c.c. of gonadotropin. Twenty-six of the 27 fluids of nonovarian cysts previously reported² were negative and fluid from one parovarian was positive for estrogen.

Comments*

Considering the part the ovary plays in the endocrine system, it is of interest to consider what role hormones might play in the etiology and development of ovarian tumors. In this study we have attempted to correlate the histology of the tumor, especially of the lining of the cyst cavity, with the hormonal findings of the cyst fluid. Considering the multiplicity of the component parts of the ovary, both endocrine and otherwise, and the intricate mechanisms involved in the rapid and successive changes which take place, it is not surprising that the ovary gives rise to a variety of pathologic developments and to neoplasms. It is of interest to consider what might happen should any one of these mechanisms fail or the hormonal state be altered by pregnancy.

In view of the striking effects on the ovary of gonadotropin from various sources, it might be possible to infer excessive hormonal stimulation as a possible contributing factor, at least, in certain types of pathologic conditions in the ovary. Such effects have been produced in both experimental animals and in human beings.²⁴⁻²⁹ Furthermore, this view might be supported by the high incidence of lutein cysts associated with hydatidiform mole and chorionepithelioma.³⁰⁻³² In these conditions the high level of gonadotropin is believed to be responsible for the luteinization of the ovary and regression³² has been observed following the removal of the mole. Since gonadotropin may be present in early pregnancy³³⁻³⁶ in amounts comparable with those found in hydatidiform mole and chorionepithelioma,¹³ it is somewhat surprising that in normal pregnancy similar changes do not occur frequently. However, the fact

*These comments are not intended to give a comprehensive review of the field and many citations have been omitted for brevity.

that in normal pregnancy the high gonadotropin level is maintained for a relatively short period may account in part for the difference. On the other hand, one might speculate concerning the high incidence of corpus luteum cysts in early pregnancy when the gonadotropin level is high.

What effect pregnancy or the hormones associated with pregnancy may have on tumors which are not known to arise from recognizable ovarian structures is largely a matter of surmise. Since the tumors are usually considered a complication of pregnancy and removed, the effect of pregnancy on their development cannot be observed over a period of time. Although it seems that the incidence of the various types may differ somewhat from that found among nonpregnant patients, it is difficult to determine definitely the age of the tumor. The high incidence of ovarian tumors occurring with the first pregnancy may possibly have some relation to the pregnancy but may merely mean that the tumors are discovered in the course of routine ante-partum examinations.

In general, the amount of estrogen in the cyst fluid was about that found in the cysts of nonpregnant patients.² This may be because the tumors were usually removed in early pregnancy when the estrogen level is low. Cysts removed post partum seemed to show more hormone. The findings would indicate also that the tumors do not store appreciable amounts of estrogen. However, two of the four dermoids removed early in pregnancy contained estrogen. This series is too small to permit very definite deductions.

Summary

Thirty cases of ovarian cysts associated with pregnancy have been investigated and the findings compared with those of a series of nonpregnant patients previously reported.

Excluding 4 dermoid cysts the incidence of the various types of cysts was: follicle, none; corpus luteum, 7 (26.9 per cent); simple serous, 6 (23.1 per cent); papillary serous 2 (7.7 per cent); pseudomucinous 11 (42.3 per cent). Although the group is too small to make definite deductions, the incidence of corpus luteum and pseudomucinous cysts seems higher than in the series of nonpregnant patients.

Twenty and eight-tenths per cent of the ovarian cysts (30 of 144) of the entire series were associated with pregnancy. Sixty-six and seven-tenths per cent of the cysts (96 of 144) were from patients with history of one or more pregnancies. Of these 40.6 per cent (39 of 96) were primiparas and the cyst was associated with the pregnancy in 56.4 per cent of the cases (22 of 39). Seventy-three and three-tenths per cent of the cysts (22 of 30) associated with pregnancy were associated with the first pregnancy.

Twenty-seven and eight-tenths per cent and 28.5 per cent of the cysts occurred in patients in the age groups 15 to 24 and 25 to 34 years, respectively. In these groups, 35.0 per cent and 34.1 per cent of the cysts, re-

spectively, were associated with pregnancy. Of the cysts removed in the decade 15 to 24 years 30.8 per cent (8 of 26 cysts) from nonpregnant patients, 50 per cent (5 of 10 cysts) from pregnant patients and 50 per cent (2 of 4 cysts) from post-partum patients contained estrogen. In the cysts from patients in the age group 25 to 34 years, estrogen was found in 40.7 per cent of the cysts (11 of 27) from nonpregnant patients, 36.4 per cent (4 of 11 cysts) from pregnant patients and 66.7 per cent (2 of 3 cysts) from post-partum patients.

Of the cysts removed during pregnancy the percentages of the various types which contained estrogen were: follicle (no cysts); corpus luteum, 71.4 per cent (5 of 7 cysts); simple serous, 25 per cent (1 of 4 cysts); papillary serous, one negative; pseudomucinous, 14.3 per cent (1 of 7 cysts); dermoid 50 per cent (2 of 4 cysts). Of the 7 cysts removed post partum, there were no follicle or corpus luteum cysts; 2 simple serous, 1 papillary serous and 1 of 4 pseudomucinous cysts contained estrogen. Forty-three and three-tenths per cent of all the cysts associated with pregnancy contained estrogen in contrast to 33.3 per cent in the nonpregnant group. Excluding follicle and corpus luteum cysts from each series, the percentages which contain estrogen were 34.8 per cent to 22.1 per cent, respectively.

Gonadotropin was found in the fluids of ovarian cysts associated with pregnancy.

Three parovarian cysts, 1 cystic fibroid and 1 cyst of Gartner's duct associated with pregnancy were studied.

We wish to express our appreciation to the members of the staff for their co-operation in supplying the clinical material.

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Ramos, A. P., Albertelli, J. F., and Colombo, E.: The Value of Quantitative Determination of Gonadotropin in the Diagnosis of Chorionepithelioma, *Rev. argent. de cien. med.* 1: 8, 1943.

The authors state that the maximum guarantees of early diagnosis of chorion-epithelioma are to be found through biologic tests. Since this neoplasm always secretes huge amounts of choriogonadotropins, the quantitative determination of these by-products, in the absence of pregnancy, is of utmost diagnostic importance. For diagnosis the presence of at least 50,000 rat units per liter are required.

The authors conclude that the existence of large amounts of gonadotropin is not essential if re-examinations of urine reveal an ascending curve following an abortion caused by a mole, or if a degeneration of the trophoblast is suspected. They carry out weekly estimates for at least two months, searching for 200 units. If this quantitative determination increases gradually to 500 or 1,000 units per liter the diagnosis can be established and treatment be instituted.

Two outstanding cases which were followed by hysterectomy and pathologic substantiation of the tumor are mentioned in this article.

CLAIR E. FOLSOME.

Matters, R. F.: Sulphonamides and Purulent Peritonitis, *M. J. Australia* 2: 85, 1943.

The author found that intraperitoneal sulfanilamide has proved most effective in cases in which the peritoneum has been infected. It is rapidly absorbed from the peritoneum within 24 hours. The gross pus must be removed before the powdered sulfanilamide is applied. The sulfanilamide does not appear to affect the healing of wounds or the normal state of the intestines.

WILLIAM BERMAN.

ENDOMETRIOSIS AND PREGNANCY

With a Report of Two Cases

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RECENTLY two cases of endometrial cysts complicating pregnancy were operated upon in this hospital. A review of the varied forms in which endometrial cysts may complicate pregnancy or be complicated by pregnancy has been stimulated by the rarity of this disease as an obstetric problem, and also, by its apparent increase in incidence.

It is not the purpose of this paper to review the subject of endometriosis. A study of the classic work of Sampson¹⁻⁸ and the more recent papers (Novak,⁹ Keene and Kimbrough,¹⁰ Payne,¹¹ Counseller,¹² Fallas and Rosenblum,¹³ Dannreuther,¹⁴ Meigs,¹⁵ Holmes,¹⁶ Haydon,¹⁷ Jenkinson and Brown,¹⁸ and others) will reveal the vast amount of research and the tremendous interest that this disorder has aroused.

The diagnosis of endometriosis is definitely on the increase, a fact which has impressed practically all recent workers in this field, many of whom give statistics as proof.

Sampson found that in 1925, 29.5 per cent of his laparotomies, 98 out of 332, showed endometriosis (quoted by Meigs¹⁵). Fallas and Rosenblum¹³ report the lowest percentage—1.62 per cent endometriosis in 15,975 gynecologic laparotomies done in two Los Angeles private hospitals from May, 1930 to April, 1939. Holmes¹⁶ had 80 proved cases of external endometriosis in 307 gynecologic laparotomies, an incidence of 26.0 per cent. The statistics given by Meigs¹⁵ in 1941 are particularly revealing. In 400 private abdominal cases, 36 per cent were considered to have endometriosis grossly, and 28 per cent showed endometriosis microscopically. This contrasts with 8.3 per cent by gross diagnosis and 5.8 per cent by microscopic diagnosis in 400 Massachusetts General Hospital ward abdominal cases.

This is statistical evidence for two important facts peculiar to endometriosis. It is definitely a social-economic disease, raining its pelvic devastation, for some unexplained reason, much more frequently upon the higher social and economic strata of womanhood. The second fact that Meigs' statistics bear out is the importance of careful gross diagnosis, because microscopic studies, necessarily somewhat incomplete, often fail to show definitely, endometriosis.

All authors are agreed that the greatest incidence of endometriosis is found in the last half of the fourth decade of life, a period of reduced fertility which is still in the childbearing age. A review of the reported cases of endometriosis and pregnancy reveals a high incidence of elderly primiparas. Internal endometriosis (adenomyosis and adeno-

myoma) is found more frequently in the early forties; it is not as commonly associated with sterility as is external endometriosis.

Combining a discussion of endometriosis and pregnancy is in some measure a paradox. Reynolds and Macomber¹⁹ give 88 per cent as the normal fertility in marriage. This contrasts with the much reduced fertility in cases of endometriosis. Counsellor¹² found that 48.9 per cent of 131 married patients with the disease had either never been pregnant, or had only miscarriages or abortions, so that the absolute sterility rate was 32.1 per cent. Payne's¹¹ series showed that 40 per cent of 238 married patients with endometriosis had never been pregnant. Haydon¹⁷ reported a relative sterility rate of 53 per cent. Keene and Kimbrough¹⁰ found absolute sterility in 40.9 per cent of 118 cases, and in the remaining cases 9.5 years had elapsed since the birth of the last child. Jenkinson and Brown¹⁸ stated that 34 per cent of their patients complained of absolute sterility. Many explanations have been offered for this relative and absolute sterility. Associated pathologic lesions of the female genitalia are very frequent, and this associated lesion may often be the indication for operation. Combining Counsellor's¹² and Masson's²⁰ series, 54.5 per cent of 844 cases of internal and external endometriosis revealed associated pelvic disorders. These disorders include myomas, endometrial hyperplasia, chronic pelvic inflammatory disease, ovarian cysts (exclusive of endometrial cysts), solid tumors of the ovary, and other disorders. These pathologic processes are all well known to be causative and contributing factors to both absolute and relative sterility. Pelvic adhesions incident to endometriosis must certainly be a factor. The most logical reason for these adhesions being a sterility factor would seem to be tubal occlusion, yet in 293 cases of endometriosis Sampson⁶ found both tubes patent in 284 cases, a strong point in his retrograde menstruation theory. A possible explanation is that adhesions about the ovary prevent the ovum from escaping or prevent it from entering the tubal lumen. A factor not sufficiently stressed in previous publications is the diminished frequency of coitus in these cases with endometriosis. Coitus is diminished because of the complaint which brings them to the physician, namely dyspareunia, metrorrhagia, menorrhagia and similar complaints.

Meigs¹⁵ approaches the subject of sterility and endometriosis from a different angle. He believes that delayed marriage, lack of early and interrupted childbearing, and the consequent persistent and uninterrupted menstrual cycle, are conducive to the development of endometriosis, particularly in the higher social and economic levels where delayed childbearing and endometriosis are most common.

Because pregnancy is frequent enough following conservative operative procedures, where conservatism is possible in endometriosis, the surgeon must always bear in mind the importance of preserving the childbearing function in these relatively sterile women. This need for conservatism calls for the finest judgment at the operating table, and no rules can be made which are applicable to all cases. The general principle only can be stated: if the disease is not too extensive and the patient is anxious to become pregnant, conservative surgery should be practiced, with the full understanding that a subsequent operation may be necessary, and that the odds for a pregnancy are long.

The surgeon must consider in what ways endometriosis may complicate pregnancy, as must the obstetrician in his differential diagnosis of obstetric problems. The two cases to be reported, and a review of the literature, prove the fallacy of Sampson's statement²: "Should a patient with this lesion become pregnant and the latter condition recognized, there would not be sufficient indications present to justify an abdominal operation." Undoubtedly many patients with asymptomatic endometriosis, minimal or moderately extensive, have uncomplicated ante-partum, intrapartum, and post-partum courses. Sampson's belief⁴ that pregnancy's influence on the endometriosis implants "lessens their incidence and the subsequent involutionary changes may possibly retard the future development, or even cause the regression, of any implants present," may well be true, but it is difficult of statistical proof.

Ectopic Decidual Reaction and Pregnancy

This subject has been very thoroughly studied, and the literature is replete with articles discussing the various anatomical sites, the incidence, and the significance of ectopic decidual formation.

Walker²¹ in 1887 was the first to describe decidua beneath the serosal epithelium of the pelvic peritoneum in a case of intra-abdominal pregnancy. Hirschberg²² in 1905, Taussig²³ in 1906, Hofbauer²⁴ in 1929, and Weller²⁵ in 1935, reviewed the subject, and they have cited instances of reported occurrence in the pelvic peritoneum, ovaries, tubes, appendix and other portions of the intestines, omentum, diaphragm, splenic capsule, and other intra-abdominal tissues, as well as in pelvic lymph nodes, cervix, vagina, and abdominal scars. Reported cases of decidual reaction in the cervix have often been associated, for some unknown reason, with placenta previa. Geipel²⁶⁻²⁸ did much work on this subject and reported many instances of its occurrence in the diaphragm (peritoneal surface), splenic capsule, and pelvic lymph nodes. He believed that the peritoneal transudate in pregnancy contained certain substances or hormones capable of producing this response. Taussig's²³ interesting theory was that the placental metabolic products escaped out of the tubes and incited the production of decidua.

As Weller²⁵ pointed out, the sites of election for ectopic decidua correspond impressively with the regions where endometriosis is most commonly found. Endometriosis and ectopic decidua formation decrease as the distance from the ovaries increases. Ectopic decidua formation on the ovaries varies from 40 per cent to 100 per cent in the cases where ovaries were examined microscopically during or immediately after a pregnancy. Harbitz²⁹ found ectopic decidua formation on the ovaries in all seven of his cases. Hofbauer²⁴ found decidual reaction on the posterior uterine surface in 15 of 23 pregnant uteri which he examined. The fact that the cellular elements immediately beneath the serosal cells may be stimulated by pregnancy to form decidual cells, and the fact that, as the distance from the ovaries increases the incidence diminishes, add weight to the Iwanhoff-Meyer serosal (celomic) heteroplasia theory of endometriosis. Olson and Hansmann³⁰ believe that the finding of ectopic decidua in the areas noted is more in accord with the Halban lymphatic-spread theory of endometriosis.

Every obstetrician and gynecologist is familiar with the gross picture of ectopic decidua at operation. The ovaries particularly present a very striking gross abnormality. Early in pregnancy there are superficial, slightly raised sheets which are reddish-white, wrinkled and velvety or there are lentil-sized nodules or flecks over the ovarian surface. Later in pregnancy these surface areas become more granular and whitish, suggestive of wax drippings. If more complete sectioning of pathologic tissue were done, ectopic decidual formation would probably be found in every pregnant case.

Ectopic decidua formation does not signify endometriosis, for endometrial glands must in addition be identified in order to apply this term properly. Most of the cases of endometriosis associated with pregnancy describe stromal decidual reaction in the microscopic studies. Those reports of ectopic decidual formation without pregnancy are probably the pseudodecidua of the late premenstrual phase.^{31, 32}

Endometriosis and Pregnancy

According to Cullen,³³ "adenomyomas" containing uterine mucosa are found in the body of the uterus, rectovaginal septum, uterine horn or tube, round ligament, ovary, uterosacral ligament, sigmoid flexure, rectus muscle, and umbilicus. Other reports have added the rectum, cecum, appendix, small intestines, retroperitoneal and inguinal lymph nodes, bladder, cervix and vagina, laparotomy scars, inguinal hernia sac or patent canal of Nuck, and even the lung. It has been the custom to divide endometriosis into the internal and external types. The internal type includes only the type limited to the uterine musculature, more commonly termed uterine adenomyoma or adenomyosis, and the external type includes all other areas containing ectopic endometrial tissue. Fallas and Rosenblum¹³ in 260 cases of endometriosis found the internal type alone in 49.6 per cent (129), external alone in 36.5 per cent (95), and combined in 13.9 per cent (36). Masson³⁴ in 576 endometriosis cases found adenomyoma of the uterus in 81.9 per cent (482), ovarian endometriosis in 13.4 per cent (77), rectovaginal in 3.5 per cent (20), and sigmoid in 2.4 per cent (14). Haydon¹⁷ in 569 cases of endometriosis found it in the ovaries in 60.6 per cent (345), uterus 55 per cent (313), cul-de-sac 33.5 per cent (191), ligaments of the uterus 12.1 per cent (69), tube 2.8 per cent (16), rectum 2.4 per cent (14), and the sigmoid, abdomen, bladder and appendix in smaller percentages. Adenomyoma or adenomyosis of the uterus is less often associated with the sterility factor, a prominent feature of cases with external endometriosis.

Internal Endometriosis (Uterine Adenomyoma or Adenomyosis)

Many of the reported cases of internal endometriosis and pregnancy represent incidental pathologic findings, and the reasons for removal of the uterus are not exactly clear, particularly in the German literature.

Amos³⁵ in 1905 reported a case of adenomyoma of the uterus with decidual reaction, a supravaginal hysterectomy being done at the time of a 5 months' intrauterine pregnancy. Robert Meyer³⁶ in the same

year described three cases of adenomyoma and pregnancy, one with decidual reaction. Sampson^{cited by 37} reported a case with a myomatous nodule on the posterior wall of the uterus which pathologically was proved to be adenomyoma with decidual reaction. Cullen³⁸ wrote of an adenomyoma of the right uterine horn; the adenomyoma showed decidual reaction and was associated with subserous and intramural myomas and an unruptured tubal pregnancy on the left side. Aschheim,³⁹⁻⁴¹ in 1923 and 1929, in three separate papers, had three cases of adenomyoma with pregnancy and decidual reaction, one being associated with an endometrial cyst of the right ovary and endometriosis of the right uterosacral ligament. The reason for laparotomy in the above cases was usually the clinical diagnosis of a myomatous uterus. The additional diagnosis of an unruptured tubal pregnancy was made in Cullen's case. It is possible that the uterine asymmetry and pregnancy could be interpreted preoperatively as a cornual pregnancy, but there are no such cases in this group.

Uterine rupture is probably the most dramatic of complications of adenomyoma of the uterus and pregnancy. A wall weakened by islands of endometrial stroma and possibly more deeply invaded by the chorionic villi, can account for uterine rupture as well as uterine atony.

Schäfer⁴² in 1918 reported a 41-year-old, para x, 7 months pregnant with twins, who upon lifting a heavy object ruptured her uterus and lost three liters of blood into the peritoneal cavity. A 10 cm. uterine rupture was found, and this area of rupture showed, microscopically, adenomyoma and decidual reaction. Richardson⁴³ in 1919 published a pathologic report of a case of spontaneous rupture of the uterus at the anterosuperior surface which showed decidual cells extending deep into the musculature at the site of rupture. Aschheim⁴⁰ cited a case of peritonitis following the performance of a criminal abortion in which the removed uterus did not show the actual perforation, but there were scattered areas of endometrial glands and stroma with decidual reaction deep in the uterine musculature. Schugt⁴⁴ in 1926 reviewed the causes of uterine rupture and described a case of a 32-year-old, para v, whose uterus he ruptured posteriorly for a length of 4½ cm. at the time of a digital completion of a 4 months' abortion. A hysterectomy was done, and at the region of the tear endometriosis was found. In addition, the original abortion had been criminal; the uterus had been perforated by an instrument at this same area, and the omentum was healing over the perforated area. Spontaneous rupture at the onset of labor was the complication of Stone's⁴⁵ case. At laparotomy a posterior uterine rent, 5 cm. long, was found, and the abdomen contained one liter of bloody fluid. Adenomyosis with decidual reaction was found around the area of rupture and elsewhere in the uterus.

Uterine atony due, supposedly, to internal endometriosis has been infrequently reported. Schweitzer⁴⁶ at the time of section for placenta previa found a tumor nodule on the posterior surface of the uterus, adherent to the sigmoid and obliterating the cul-de-sac of Douglas. A hysterectomy was done because of uterine atony (a not uncommon added complication of placenta previa), and the tumor was found to be an adenomyoma with decidual reaction. Szene's⁴⁷ post-partum hemorrhage case after a normal delivery was followed by a vaginal hysterectomy. The pathologic finding was adenomyosis and decidual reaction one-third of the distance through the uterine wall at the placental

site. Sackett⁴⁸ explained the uterine atony at a second cesarean section necessitating hysterectomy upon a large number of endometrial islands with decidual reaction, in the myometrium.

An adenomyoma in the lower uterine segment could easily be interpreted clinically as a myoma, and a section performed because of suspected or evident dystocia. Lochrane⁴⁹ did a section on a 42-year-old primipara because of a tumor the size of a tennis ball on the posterior uterine wall and because of a breech presentation. The tumor was an adenomyoma with decidual reaction. Josselin de Jong and de Snoo⁵⁰ described a tumor filling the cul-de-sac of Douglas, grossly suspected of being a sarcoma, in a 39-year-old, para i, patient. The section was done because of the danger of uterine rupture. The tumor was removed, found to be an endometrial tumor which had "grown-into" the uterine musculature, but no connection could be found with the endometrium. Ectopic decidual reaction was found, in addition to its presence in the tumor mass, in both ovaries, both broad ligaments, the left round ligament, and the right tube. It is not altogether clear from the report whether this should be considered an adenomyoma of the uterus or a cul-de-sac endometriosis. Schweitzer's⁴⁶ case mentioned above could very likely have had serious dystocia from the tumor nodule on the posterior surface of the uterus, had it not been complicated by a placenta previa and had vaginal delivery been attempted. In addition to Schweitzer's report of adenomyoma and placenta previa, J. Whitridge Williams⁵¹ reported a case in 1904 which died when 6 months pregnant from a central placenta previa. Autopsy showed extensive adenomyosis with decidual reaction in both the anterior and the posterior uterine walls.

Sampson's⁷ case of ectopic pregnancy was quite unusual. His patient had had a ventrofixation of the uterus and an attempted tubal sterilization, subsequent to which she developed an ectopic pregnancy in an area of endometriosis at the left uterine cornu.

The statement has been glibly made that abortions and miscarriages may be due to uterine adenomyosis or adenomyoma. Any uterine lesion may increase the incidence of abortions, but statistical proof of the role played by internal endometriosis is wanting.

In twelve of the above cases the age is available. The average age was found to be 36.1 years. In ten of the cases the parity was given. Four were primigravidas, two para i, and one each were para ii, iii, v, and x respectively.

External Endometriosis and Pregnancy

External endometriosis, as previously defined, includes all cases of endometriosis exclusive of those involving the uterine musculature from within. A classification of such endometriosis cannot be exact, for in many instances the lesions overlap from one area into another. For example, posterior cul-de-sac endometriosis may be a part of, or in stages become, endometriosis of the rectovaginal septum and vaginal endometriosis. External endometriosis may be found on the pelvic peritoneal surfaces, the uterine ligaments, ovaries, tubes rectovaginal septum, vagina, cervix, intestines (appendix, small and large intestines),

hernial sacs, umbilicus, abdominal scars, vulva, pelvic lymph nodes, and even lungs.

In reviewing the cases of endometriosis and pregnancy many examples of the posterior cul-de-sac or rectovaginal septum and the ovarian groups are found, but in the other groups only an occasional, isolated report is found. This is in accord with what would be expected from consideration of the relative frequency with which endometriosis is found in the various areas, and in accord with the pathologic picture most liable to produce symptoms if complicated by pregnancy.

Eleven cases of posterior cul-de-sac or rectovaginal septum endometriosis and pregnancy were found in the literature. Many of these reports were sketchy and were reported before delivery of the pregnancy which was under consideration. Griffith⁵² in 1913 was the first to report a case. His case was a 37-year-old patient with one previous pregnancy who, when examined at 5 to 6 months of a gestation, was found to have a cervix fixed by an ill-defined mass between it and the rectum. Biopsy of the vagina over this mass, taken in an area of soft and spongy tissue which bled easily upon trauma, showed endometriosis with decidual reaction. The lesion increased in size over the following month; radium was applied, and by one month from term the mass was much smaller and probably offered no dystocia to vaginal delivery. Lochrane⁵³ in 1922, described finding an irregular nodule imbedded in the posterior vaginal fornix of a 33-year-old primigravida, 18 to 20 weeks pregnant, who had had bowel bleeding. A biopsy at this time and eight weeks later was reported as adenomyoma with decidual reaction. Ulesko-Stroganowa⁵⁴ encountered a lentile-sized rectovaginal tumor, causing bleeding from the rectum, in a patient ten weeks pregnant; adenomyoma with decidual reaction showed microscopically. The subsequent course of this patient was not given. Josselin de Jong and de Snoo's⁵⁰ case in 1925, aged 39 and para i, was sectioned because of an abnormal presentation and the finding of a tumor mass behind the vaginal vault. The growth posterior to the uterus was thought at operation to be a sarcoma and was surgically removed, only to find on examination, endometriosis with extensive pelvic decidual reaction. The mass was stated to have invaded the uterus, but from description it seemed most likely to have been of cul-de-sac origin. Haselhorst⁵⁵ in 1933 excised a small nodule from the posterior cul-de-sac of a 27-year-old patient and diagnosed by the decidual reaction in an area of endometriosis, a very early pregnancy. Otto von Franqué⁵⁶ reported in 1934 two cases of endometriosis and pregnancy. The first case was a 39-year-old, para ii, who three years prior to delivery had a walnut-sized nodule between the rectum and the cervix, proved by biopsy to be endometriosis. She was delivered of a 3,620 Gm. fetus by difficult forceps and Dührssen's incisions. Von Franqué did not feel that the difficult delivery was related to the nodule, because the nodule had become smaller than walnut-size early in pregnancy.

Szymanowicz's⁵⁷ patient, 41 years old, had a tumor which was finger-size between the cervix and the rectum, producing postcoital bleeding and showing histologically endometriosis. She returned fourteen months later, at which time she was two months pregnant, and the tumor mass was smaller and continued to diminish in size as the gestation advanced.

She had a normal delivery⁴ and puerperium, and when examined one month after discharge, no tumor could be felt. Hay,⁵⁸ in 1939, reported the removal of a polypoid mass (2 by 1 in.) per vaginam, arising in the rectovaginal septum and causing dyspareunia and leucorrhea. She was 25 years old, had been married for 6 months, and at the time of removal was overdue for her menstrual period. The mass had doubled in size in the two weeks before removal. Pathologically, the tumor was endometriosis with decidual reaction. The mass again grew to its original size during the ensuing month, and at about the sixteenth week of the gestation began to recede in size. At a later interval in the pregnancy it was the size of a fifty-cent piece and 1 cm. thick. She was sectioned electively, and at operation no cul-de-sac endometriosis was found. Twelve days postoperatively the vaginal lesion was biopsied, again revealing endometriosis, but no decidual reaction. Four months following delivery she was again pregnant, and the area of endometriosis, as previously, grew larger and later began to recede. In the eighth month of this gestation she was again sectioned, this time because of a twin pregnancy. Five months after this operation, several shotty nodules were found in the rectovaginal septum which showed the same histologic picture of endometriosis. This case is a striking contradiction to the statistics showing a high absolute and relative sterility rate in endometriosis, for here we have a 27-year-old female who has been married for less than two years, with three children, all under one year of age.

Batizfalvy,³⁷ in a review of the subject, described his case of a 26-year-old female who had rectovaginal endometriosis, proved by biopsy. She was irradiated, and a temporary amenorrhea resulted. She then became pregnant, and the lesion increased in size, and ulcerated. A section-hysterectomy was done one month from term. The ovaries were conserved at the operation, and a follow-up history revealed that she had vaginal bleeding regularly every month, in addition to postcoital metrorrhagia.

Portes, François, and Varangot,⁵⁹ and later Portes and Varangot⁶⁰ in a review of endometriosis and pregnancy, reported a patient who was 32 years old and who had had one miscarriage. She began to notice vaginal bleeding in the seventh month of her second pregnancy. Upon examination an ulcerating tumor mass was found extending into the vagina from the posterior cul-de-sac. The mass was the size of a large "nut." A biopsy of the tumor mass was reported as "spinal cell epithelioma of the vagina." The patient was delivered by section-hysterectomy, and four days post partum a biopsy of the vaginal tumor showed endometriosis. Vignes,⁶¹ in a discussion of the above case, cited a 28-year-old multipara, who had a rectovaginal endometriosis and whose pregnancy terminated with an abortion at 22 weeks. The nodule was later excised, returned in two months, and the recurrence was irradiated. Sixteen months after the application of radium she delivered a 30 weeks premature infant. Two months after this delivery the rectovaginal septum was hard, but no definite tumor mass could be felt, despite the fact that four days post partum an egg-sized, tender mass was felt in this region.

The second most frequent site for endometriosis complicating pregnancy is in the ovary. It is in this group that the two new cases reported in this paper belong. Ovarian endometriosis is much more common than cul-de-sac endometriosis, yet case reports of ovarian endome-

triosis complicating pregnancy are relatively rare. The difficulties of accurate palpation of the ovaries in the presence of an intrauterine pregnancy may account for some of the scarcity of reported cases. All too frequently cursory pelvic examination (or even no pelvic examination!) of prenatal patients is done, and many endometriosis cases are missed or the findings interpreted as salpingitis. Many small endometrial cysts are followed throughout pregnancy, cause no complications, and the association is never realized.

Sampson²⁻³ in 1922 reported the first case of pregnancy and ovarian endometriosis. His patient was 37 years old and had never previously been pregnant. A laparotomy was done for a myomatous uterus, and at operation a cyst, 2 cm. in diameter, filled with chocolate material, was found in the left ovary. Decidual reaction was found in the lining of this cyst, as well as in an endometrial implant on the posterior uterine surface. The uterus contained a fetus, 14 mm. long.

Winestine⁶² in 1924 described a patient, 35 years old, who had an oophorecystectomy performed in early pregnancy because of left lower quadrant abdominal pains, chills, and fever. An endometrial cyst, the size of a hen's egg, showing decidual reaction in the wall, was found in the left ovary. There is no very satisfactory explanation in this case report of the patient's presenting complaints. Asehheim's⁴¹ case in 1929 of a right ovarian endometrial cyst was described under internal endometriosis, for the ovarian cyst was an incidental finding.

Shaanning⁶³ in 1930 reported an adherent endometrial cyst of one ovary removed from a 29-year-old patient, sixteen to eighteen weeks pregnant. Von Franqué,⁵⁶ in addition to the cul-de-sac endometriosis case, in 1934 described a fist-sized ovarian endometrial cyst which had been removed from a 28-year-old patient five to six weeks pregnant. At operation von Franqué's case showed cul-de-sac thickening. The patient's presenting complaint was leucorrhea, and she aborted the pregnancy on the thirty-eighth postoperative day.

Ramos⁶⁴ in 1940 detailed a patient, 27 years old, who had had the second criminal abortion. Because of continued vaginal bleeding a laparotomy was done, and an egg-sized cyst was removed from the right adnexal region, and a nut-sized cyst was resected from the left ovary. The right ovarian cyst was definitely endometrial, but the left adnexal mass was not described microscopically. McKenzie⁶⁵ in 1943 had an interesting patient, 25 years old, who showed, in the same ovary, endometriosis and a ruptured ovarian pregnancy. This patient, from the operative description, also had cul-de-sac endometriosis.

Although ovarian cysts of endometrial origin have been termed "perforating, chocolate cysts" by Sampson, it is strange that so few cases of severe and sudden rupture of these cysts and a resulting "surgical abdomen" are reported. The cyclic hemorrhage and increased intracystic pressure would seem to offer good potentialities for such an accident. The usual process seems to be an occasional leak with rapid walling-off by reactive inflammation, and later, extensive adhesions. A laparotomy is rarely performed as the symptoms are usually of transient duration and are seldom sufficiently severe. It is usually the persisting

discomfort and other symptoms of endometriosis which bring the patient to the surgeon.

Novak⁹ in 1931 reported 3 cases of his own who were found to have had endometrial cysts which spontaneously ruptured. The preoperative diagnosis in two cases was acute appendicitis, and in the other, ovarian cyst with twisted pedicle. Novak was able to find only one similar case in the literature, a case recorded by Lee,⁶⁶ which was not accompanied by microscopic confirmation of its endometrial origin.

Because of the lack of cyclic hemorrhage into the cyst, leakage and frank rupture of an endometrial cyst would seem less common during pregnancy. Unusual pressure, and the break-up of adhesions by an enlarging uterus, are factors that might lead to such leakage and rupture. Spontaneous rupture of an endometrial cyst in the third trimester of pregnancy was the first of the two cases encountered in this hospital. The second case, a large ovarian cyst in the first trimester of pregnancy, represented an endometrial cyst with evidence of leakage, but no definite rupture.

Case Reports

CASE 1.—(History number 161381, Gyn. Pathology number 56338). This was a 25-year-old white female who registered in the obstetrical dispensary on August 17, 1942. She stated that her last menstrual period was June 6, 1942, making her due by dates for this delivery on March 13, 1943. She had been married six years, no contraception had been used, and she had been unable to become pregnant. At the time of her dispensary visit and also postoperatively, she denied abnormal vaginal bleeding and dysmenorrhea. Physical examination and laboratory studies were not revealing except for the pelvic examination. The uterus was found to be enlarged to about the size of a three months' pregnancy. On the anterior surface of the uterus was a firm, subserous nodule, about 2 cm. in diameter. In the region of the left ovary was a 4 to 5 cm. adherent, firmly cystic mass. The right ovary was thought to have been felt and was thought to be normal. The impression, in addition to the intrauterine pregnancy, was a small myoma of the uterus and ovarian cyst, left. Because of the lack of symptoms and the long period of sterility, it was considered advisable to follow the patient carefully and institute any necessary treatment later.

She was checked at frequent intervals in the out-patient department, and the antenatal course, until the episode demanding admission, was essentially uneventful, except for a transient right lower quadrant pain on October 28, 1942, unaccompanied by abdominal tenderness or tenderness on rectal or pelvic examination.

On February 9, 1943, she reported to the accident room, stating that about 8 hours previously she had been seized with a sudden, severe, sharp, and nonradiating right lower abdominal pain. The onset of this pain was while straining at stool; she had been constipated for three days. The pain continued and was accompanied by slight nausea, but no vomiting and no urinary symptoms. On examination there was an estimated 2,000 Gm. fetus in right occipito-anterior, vertex floating, and fetal heart regular in the right lower quadrant. There was no muscle

spasm or rigidity in the abdomen, but there was tenderness in the right lower quadrant of the abdomen extending from a level with the umbilicus almost to Poupart's ligament. Rebound tenderness and motion of the uterus referred pain to the right lower quadrant. The previously diagnosed myoma and ovarian cyst were not felt, and by rectal examination the cervix was long and closed and there was slight tenderness high on the right. The temperature was 99° F., and white blood count was 17,000. The other laboratory studies were within normal limits.

She was observed for sixteen hours without any particular change in her condition. The white blood count taken at intervals varied between 14,400 and 18,500 and the temperature was never above 99.2° F. The following possibilities were entertained: (1) Twisted ovarian cyst, (2) acute appendicitis, and (3) degenerated myoma. Because appendicitis could not be ruled out an immediate exploratory operation was decided upon. Under gas-oxygen-ether anesthesia a McBurney incision was made. Immediately upon entering the peritoneal cavity a moderate amount of brownish-black, semisolid material was encountered. The right ovary was felt as an elongated, raised area firmly attached to the posterior surface of the uterus, and the ovarian surface was made irregular by firm, small, tubercle-like granules. An appendectomy was done, the McBurney incision closed, and a midline incision made. A classical cesarean section incision was made and a 2,280 Gm. female child in fair condition was extracted. On the lower portion of the anterior wall of the uterus was a 2.5 cm. myomatous nodule projecting subserously. The uterus was delivered. The right ovary was found to be elongated and flattened, adherent to the posterior surface of the lower uterine segment. The adherent tissue became very thin at the peripheral points of attachment of this ovary, and at one point adherent bands were nonexistent, and brownish-black substance was escaping.

This material was found in the cul-de-sac and disseminated far down on the right anterior portion of the abdomen. Loops of rectosigmoid were adherent in the posterior cul-de-sac. The left ovary was also adherent and elongated at a higher level on the uterus, its distal portion converted into a purplish cyst about 6 cm. in diameter (Fig. 1). This cyst was later found to be filled with chocolate material. Because of the extensiveness of the lesion, typically endometrial, it was decided that a bilateral salpingo-oophorectomy and subtotal hysterectomy was the procedure of choice. This was done. The patient received intravenous fluids, plasma, and blood during the operation and was returned to the ward in good condition.

She had an uneventful postoperative course. The temperature never rose about 100.2° F., and she was discharged on the fifteenth postoperative day. The baby was discharged on the twenty-fifth day with a weight of 2,580 Gm. At 6 weeks post partum, pelvic examination revealed the cervical stump well suspended with a slight induration to the left of the suspended stump. She has been followed in the gynecology dispensary with menopausal symptoms which have been successfully treated with stilbestrol and phenobarbital.

A complete pathologic study of the specimen revealed a post-section uterus, lined with decidual tissue. The small subserous nodule was a typical fibromyoma. There was an extensive decidual reaction over the posterior surface of the uterus (Fig. 4). Both the right and the left endometrial cysts were found to be lined with fragmented cuboidal

epithelium, beneath which there was a narrow zone showing endometrial stroma with irregular groups of decidual cells dispersed throughout this stroma, and numerous pigment-laden macrophages. The walls of the cysts peripheral to the endometrial tissue showed a narrow zone of ovarian stroma. These were noted grossly over the surface nodules which proved, microscopically, to be of decidual tissue, and which were of a much more fibrous character than the usual decidual tissue (Figs. 2 and 3). These nodules were found over the surface of both ovarian cysts. The tubes were normal and the appendix showed no lesions.

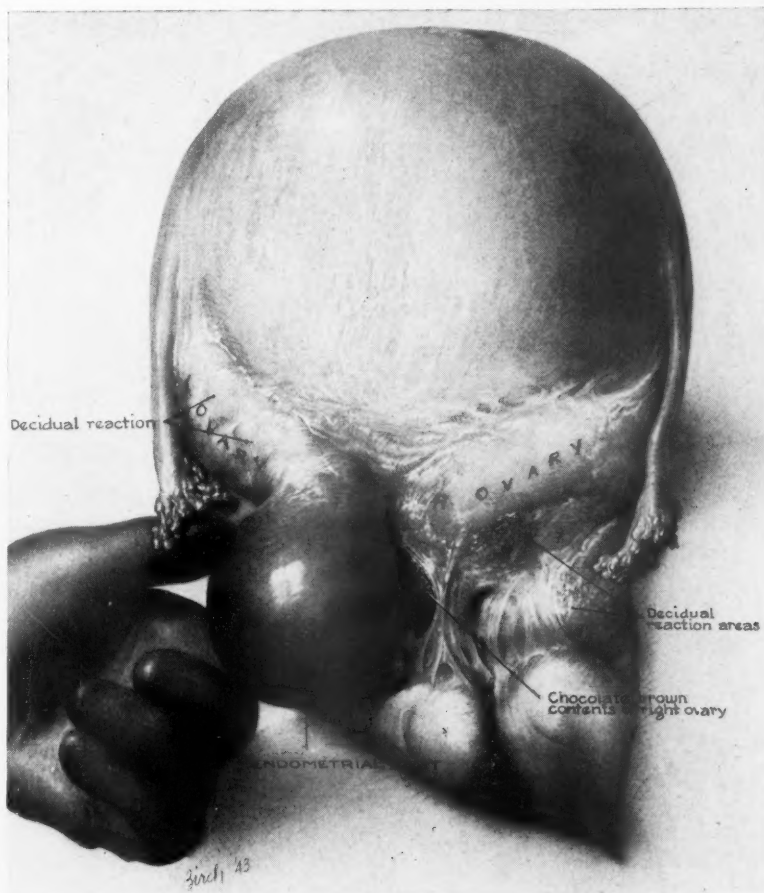


Fig. 1.—(Case 1.) A drawing of the gross specimen as viewed from the posterior aspect at the time of operation. The pregnant uterus and normal tubes are seen. The left ovary is elongated and adherent with the distal end converted into an endometrial cyst. The right ovary and ovarian cyst are firmly attached to the uterus, and the point of rupture is seen. The surface decidual reaction is shown over both ovaries, and there are intestinal adhesions posteriorly.

This was a 25-year-old primigravida who was known to have an ovarian cyst early in pregnancy. She underwent an exploratory laparotomy at 36 weeks because of severe right lower quadrant pain. A ruptured right endometrial cyst was found, and in addition there was a left endometrial cyst. A 2,280 Gm. female child which survived was delivered by cesarean section, and a subtotal hysterectomy, bilateral



Fig. 2.—A low power cross section of the right endometrial cyst wall in Case 1, showing on the left side the surface decidual reaction and on the right side of the section the internal cyst wall surface.



Fig. 3.—A high power study of the ovarian surface decidual reaction with nodules in Case 1.

salpingo-oophorectomy, and appendectomy were done. The patient made an uneventful recovery.

This patient had six years of sterility, but despite close questioning postoperatively she denied dysmenorrhea, abnormal uterine bleeding, lower abdominal pains or other symptoms commonly associated with endometriosis. A review of the operative findings (Fig. 1) reveals the probable cause of the rupture of this endometrial cyst: the cyst was adherent to the uterus and as the uterus enlarged with pregnancy the peripheral adherent areas of the cyst thinned out until they became separated, allowing contents of the cyst to escape.

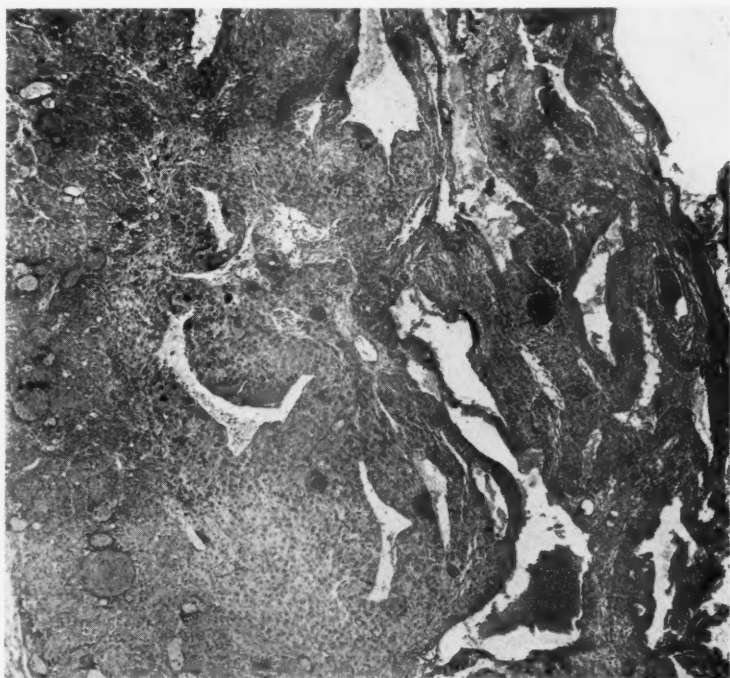


Fig. 4.—A section of the ragged, lower posterior uterine serosal surface in Case 1. The decidual reaction can be seen in one compact zone and also scattered in the adherent strands of tissue.

CASE 2.—(History number 285043, Gyn. Pathology number 56357.) This was a 23-year-old white female who was first seen by Dr. Richard TeLinde on February 2, 1943. She stated that her last menstrual period lasted for three days beginning November 22, 1942, and that this period was scant. For the month previous to being seen she had experienced some aching discomfort in both lower quadrants of the abdomen, with greater discomfort on the left side. She had been married two years and had used no type of contraception. The menstrual history had previously been quite normal, and she had had only minimal dysmenorrhea. There were no previous episodes of lower abdominal pain. This was her first pregnancy.

On examination there was a rounded, cystic mass filling up the right lower quadrant of the abdomen, and by pelvic examination this was thought to be an ovarian cyst, arising from the right ovary. The cervix

was soft, and the uterus was moderately enlarged and pushed to the left. The left ovary was not felt. There was a small Bartholin cyst on the right side. Laboratory studies were within normal limits. The impression was ovarian cyst, right, and pregnancy, intrauterine.

On February 12, 1943 under sodium pentothal-ether anesthesia a laparotomy was done. Upon opening the peritoneal cavity a cyst, about the size of a grapefruit, presented itself. This cyst replaced the right

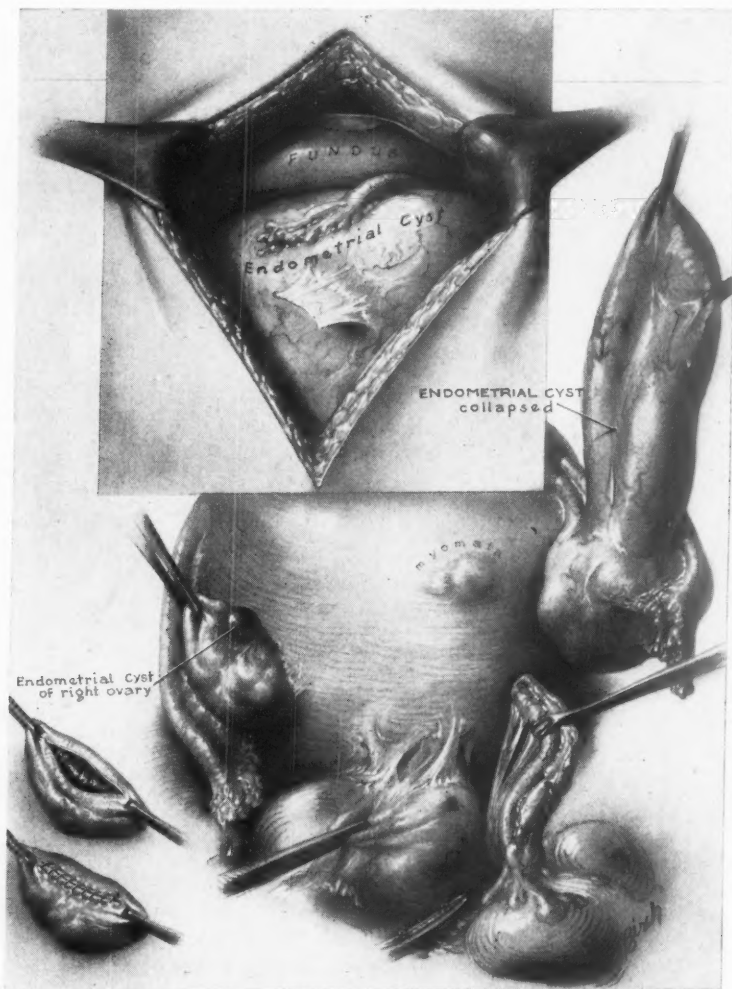


Fig. 5.—(Case 2.) At drawing at the operating table, showing the pregnant uterus, small subserous myomata, the large right endometrial cyst, and the small left endometrial cyst. The adherent intestines are represented with their small surface purplish reaction. A right salpingo-oophorocystectomy, resection of the cyst of the left ovary, and appendectomy were done.

ovary, was thick-walled and covered with shaggy adhesions, and was adherent to the posterior surface of the uterus and to the base of the broad ligament. There was a small amount of brownish, chocolate material scattered over the pelvis, and the serosa of the sigmoid colon, rectum, and appendix showed evidence of irritation presumably from this substance. The left ovary was about one and one-half times normal

size, and there was one dark, hemorrhagic area, about one cm. in diameter, on its superior surface. The tubes were perfectly normal, and the uterus was softened and enlarged to the size of a 12 weeks' pregnancy. On the posterior surface of the uterus there was a subserous myomatous nodule about one cm. in diameter (Fig. 5). A right salpingo-oophorectomy, resection of small cyst of the left ovary, and appendectomy were done. The large cyst was ruptured upon attempting to release it from its adhesions and about 300 to 400 c.c. of chocolate-colored material escaped.

Microscopically the large right ovarian cyst and the smaller cyst resected from the left ovary showed a poorly preserved lining of flattened epithelium, with, beneath this lining a narrow zone of endometrial stroma, many areas of which were converted into decidual tissue (Figs. 6, 7 and 8). There were numerous pigment-laden macrophages scattered through this same zone. The remaining portions of the walls of these cysts showed a few active, though compressed, ovarian elements.

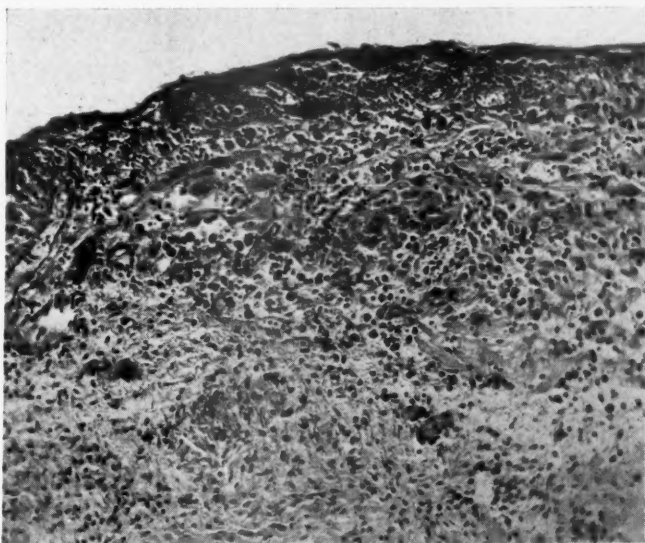
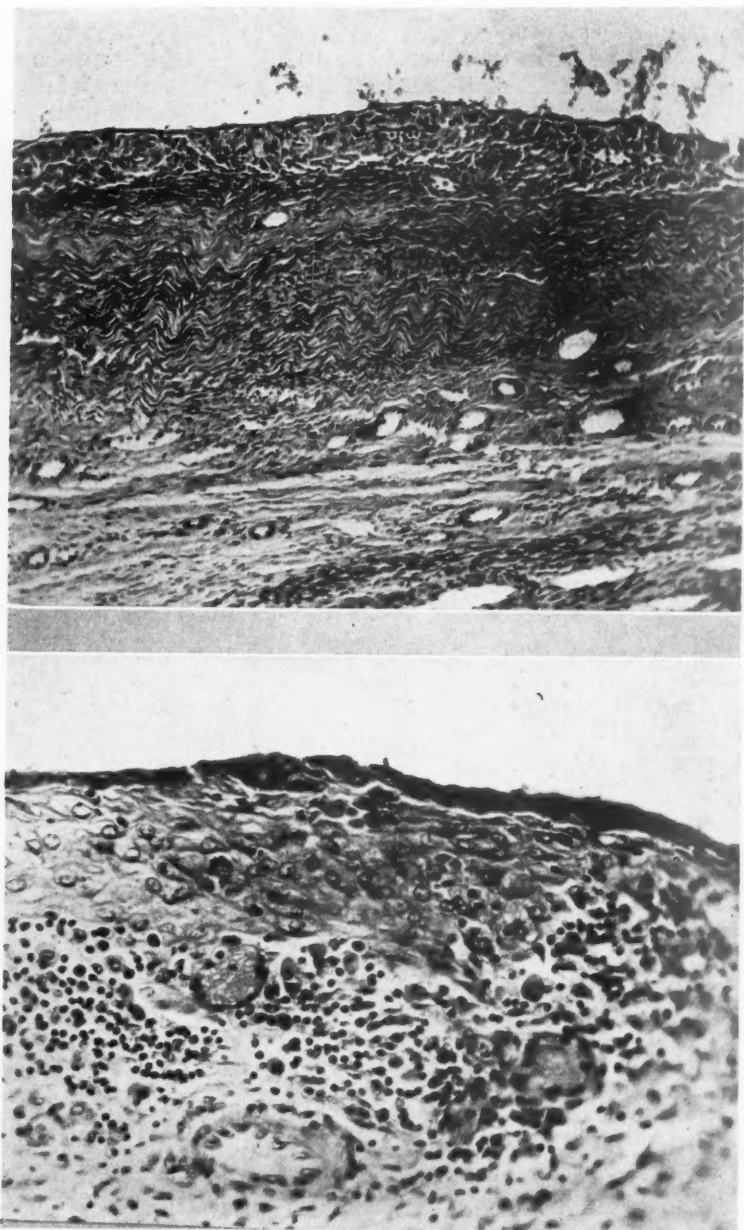


Fig. 6.—The inner surface of the right ovarian cyst in Case 2, showing the scattered decidual reaction and the cellular infiltration.

No decidual nodules were found on the surfaces of these cysts. The right tube was normal microscopically, as was the appendix.

The patient had an uneventful postoperative course and was discharged from the hospital on the seventeenth postoperative day. The corpus luteum of pregnancy was not recognized at operation and was not found microscopically. She was given proluton 5 mg. (hypo) twice daily for the first ten postoperative days. At no time did she show any evidence of threatened abortion.

The patient had an essentially normal antenatal course. She fell into labor spontaneously during the thirty-fifth week of the gestation and was delivered of a 2,390 Gm. male child in good condition, by indicated low forceps after a total labor of 2 41/60 hours. The blood pressure was normal and the urine showed no albumin. There was moderate ante-partum and intrapartum bleeding, and the placenta showed a small area of premature separation.



Figs. 7 and 8.—Low and high power studies of the left ovarian cyst wall, demonstrating the epithelium lining the cyst and the underlying decidual reaction and ovarian stroma.

Summary

This is a 23-year-old white female who had a grapefruit-sized endometrial cyst of the right ovary removed and a small endometrial cyst resected from the left ovary when 10 to 12 weeks pregnant. At operation there was a small amount of free, chocolate material scattered over the pelvis, and the patient had experienced some lower abdominal discomfort for about one month before operation. Both endometrial cysts showed areas of decidual reaction. She subsequently delivered precipitously a 2,390 Gm. male child in good condition during the thirty-five week of the pregnancy, and the placenta showed a small area of premature separation.

This patient had experienced no symptoms of endometriosis prior to the pregnancy. She had been married two years and no contraception had been practiced. Her only symptom was discomfort of an aching type in the lower abdomen, and the endometrial cyst had been "leaking," but frank rupture had not taken place.

There are other isolated reports of endometriosis associated with pregnancy found in less common sites.

Rushmore⁶⁷ in 1931 described a patient, 26 years old, who had been delivered four years previously by version and extraction and who reported, early in pregnancy, a brownish vaginal discharge. A small, polypoid mass, $\frac{1}{4}$ inch in diameter, was found just to the right of the cervical os, and biopsy showed endometrial glands and decidual reaction, superficially covered with squamous epithelium. The mass increased two to three times its original size over the subsequent eighteen days, bleeding from the nodule increased, and the pregnancy was interrupted. The pregnancy incidentally was in one horn of a bicornate uterus. Rushmore attributed the cervical endometriosis to the previous version and extraction. Zacherl's⁶⁸ case of decidua in a cervical polypoid mass of a 25-year-old patient, eight weeks pregnant, probably represented another case of cervical endometriosis.

Olson and Hansmann³⁰ did a low cervical cesarean section on a 41-year-old primigravida with a contracted pelvis and fourteen hours of labor. Shotty tubercles were found in the anterior cul-de-sac which revealed microscopically endometrial glands with a wide cuff of decidual cells.

Milnor and Tilden⁶⁹ removed an inguinal, thin-walled cyst from a 38-year-old toxemic patient upon whom they did a therapeutic abortion. The inguinal tumor had enlarged and caused increasing discomfort with pregnancy. This patient had had one living child and two previous therapeutic abortions. The cyst wall revealed endometrial stroma and nodules of decidual cells and also decidual cells were found ectopically on the appendix.

Jenkinson and Brown¹⁸ made a special study of endometriosis of the rectum and sigmoid colon. Intestinal endometriosis is infrequent; intestinal endometriosis of the small intestines is very rare. Hauffer's⁷⁰ case represents one of the most dramatic of all the cases reviewed. A diagnosis of acute appendicitis was made in a 30-year-old patient who was 6 months pregnant. A generalized peritonitis was found, originating from a perforation of the small intestine, and 17 cm. of small intestine was resected. A 2-cm. "knot" in the intestinal wall at the site of the perforation showed decidual reaction in an area of endometriosis.

Endometriosis in postoperative scars was found in 31 instances at Mayo Clinic by Wyrens and Randall,⁷¹ according to their report in 1941. Martin, Michon, and Pigeaud⁷² in 1933 stated that an endometriosis of a section scar grew with a new pregnancy. His patient was 37 years old. Harbitz²⁹ has collected a tremendous number of original and literature cases of abdominal scar endometriosis. He described a patient, 34 years old, who four years after a cesarean section had endometriosis of the abdominal scar excised. The painful lump again recurred, but three years later, during a pregnancy, the pain in the scar endometriosis entirely disappeared. The area was subsequently excised for the second time.

The average age for twenty-five of the preceding cases, in which the age was given, and including two new cases reported in this article, was 31.5 years. In eight of the cases the parity was not given, six were pregnant for the first time; seven had had one previous, one had three previous, one eleven previous pregnancies, and two were listed only as multiparas.

Conclusions

Despite the relative and absolute sterility statistics so frequently given for patients with endometriosis, the collected series of internal and external endometriosis cases complicating pregnancy is evidence enough that such patients can and do become pregnant. This fact alone should deter physicians from painting too black a picture to these patients as regards future childbearing. It should enhance the plea, so often given, that whenever possible, and particularly when the patient desires preservation of the childbearing function, to be conservative in the surgical procedure. This necessarily demands an intimate knowledge of the patient, a comprehension of her emotional and intellectual make-up, as well as a sufficiently accurate preoperative diagnosis in order that possibilities may be considered and discussed with the patient. Such a surgeon-patient relationship is fundamental, yet as surgical mass production clinics increase and socialized medicine becomes nearer to being a reality, this contact is the hardest kind to maintain. Let this one small voice enter a note of hope that somewhere, somehow, a suitable compromise may be found.

Undoubtedly, many cases of unrecognized endometriosis become pregnant and deliver without complications serious enough to warrant a procedure that would definitely establish the coexistence of the two processes, one pathologic and the other physiologic. On the other hand, gynecologists and obstetricians should be familiar with the ways in which endometriosis may manifest itself during pregnancy, and therefore, should include this disorder in their list of "possible causes."

Internal endometriosis (adenomyoma or adenomyosis) may cause an asymmetry of the uterus, indistinguishable from myomatous changes, or from a cornual pregnancy. It is, possibly, a reason for spontaneous rupture early or late in pregnancy, or may be the factor, on rare occasions, for uterine perforation at the time of therapeutic or criminal abortion. Internal endometriosis was the explanation for uterine atony

and post-partum hemorrhage in three cases in the literature. The tumor mass may be a dystocia factor, necessitating operative delivery. There is some evidence, admittedly scant, that this type of endometriosis is an element in the production of spontaneous abortions and miscarriages, ectopic pregnancies, and placenta previa. Endometriosis is sometimes partially to blame for these accidents, merely because it represents a uterine abnormality and not because of any special peculiarity of the pathologic process.

External endometriosis complicating pregnancy is most commonly found, according to the literature, in the cul-de-sac of Douglas. Usually this is symptomatic because of a vaginal extension, and the patient complains of a brownish or frankly bloody vaginal discharge during the pregnancy. Such a complaint was also given in those cases with cervical endometriosis. It is obvious that such a patient could be erroneously diagnosed as having a threatened or inevitable abortion, and unless speculum vaginal examinations and a sterile pelvic examination are done, the treatment may be disastrous to the patient and to the pregnancy. A biopsy should be obtained, in which case the pathologic process is proved. The biopsy is proof only if properly interpreted by a competent gynecologic pathologist, for in one of the previously reported cases the lesion was interpreted as a "squamous epithelioma of the vagina." A palpable mass may be found in the cul-de-sac which might give some concern as a dystocia factor during labor. According to the cases reviewed these masses are seldom of such a size as to cause any obstruction to delivery; they are often spongy and pliable, and although they frequently increase in size for the first four months, they generally become smaller in the last half of pregnancy.

Ovarian endometriosis, the second most commonly reported type found during pregnancy, is clinically recognized in several ways. An ovarian cyst may be palpated during pregnancy, and unless there are very definite complaints in the history suggesting endometriosis (a situation strikingly rare in the cases in the literature and in the two cases reported in this article), the fact that the cyst is endometrial will probably escape notice. If a laparotomy is decided upon, depending upon the individual case indications, the diagnosis can be made from the associated "tell-tale" pelvic findings and from the pathologic studies. If these symptoms are observed throughout pregnancy, it is unlikely that in the absence of cyclic endometrial changes the cyst will enlarge. The cyst may produce symptoms because of slow and occasional leaking, produced, not by intermittent hemorrhage into the cyst with increasing tension, but by increased countertension by the enlarging uterus upon an already tense cyst. Such was the situation found in Case 2 in this report. Another more sudden and dramatic episode of acute abdominal pain can result from an actual rupture of the cyst and extensive peritoneal irritation. Endometrial cysts are usually adherent and con-

sequently less amenable to intra-abdominal adjustment. They may be attached to the uterus, as was the cyst which ruptured in Case 1. In this case, as the uterus enlarged, the adherent bands of the endometrial cysts were unable to stand the increased pull and separation, and either a slow leak or a sudden escape of all of the cyst content was the result. The fact that the cysts are usually adherent explains the infrequency with which they twist. Certainly, many endometrial cysts are coincidental and the pregnancy proceeds uncomplicatedly to a normal delivery and puerperium without the patient or the physician being aware of the cyst's existence. For the peace of mind of the obstetrician and the patient and for the welfare of the pregnancy, this situation is often a fortunate one.

When encountered during pregnancy, endometriosis of the external type outside the cul-de-sac of Douglas and the ovarian regions is usually an incidental finding, and symptoms are rare. An abdominal scar endometriosis is usually asymptomatic during pregnancy, except possibly for slight enlargement. An inguinal endometrial cyst was reported to have enlarged during pregnancy. Mention should be made of the coincidental findings of tubal and ovarian pregnancy associated with tubal and ovarian endometriosis. Peritonitis following intestinal rupture through an area of endometriosis in the small intestine during pregnancy is certainly a rare, almost "freak," case.

Finally, let every gynecologist and obstetrician realize that patients with endometriosis *can* and *do* become pregnant, that this endometriosis *can* and *does* cause symptoms during pregnancy, and that in the surgical treatment of endometriosis preservation of the childbearing function *should* always receive consideration.

Discussion

1. Endometriosis, or at least the diagnosis of endometriosis, is on the increase. The greatest incidence of endometriosis is found in the latter half of the fourth decade of life, and its selectivity for the higher social-economic strata of society is shown by Meigs' statistics of 36 per cent gross diagnosis in private abdominal cases as compared to 8.3 per cent gross diagnosis in the ward abdominal cases at Massachusetts General Hospital.

2. A discussion of endometriosis and pregnancy is in some measure a paradox. Eighty-eight per cent is the normal fertility rate in marriage, according to Reynolds and Macomber. Counseller found 48.9 per cent relative and 32.1 per cent absolute sterility in 131 married endometriosis cases. Other authors have found a similar high sterility rate in their groups of endometriosis cases. Associated pathologic processes, such as myomas, endometrial hyperplasia, etc., are common. The dyspareunia, metrorrhagia, and menorrhagia found in endometriosis may serve to reduce the frequency of coitus.

3. Ectopic decidual formation is discussed, and the similarity in its distribution to the distribution of endometriosis is pointed out—both diminish in incidence as the distance from the ovaries increases.

4. Endometriosis is divided into internal and external types, according to the location of ectopic endometrial tissue inside or outside the uterine body musculature.

5. Several cases of internal endometriosis (adenomyoma or adenomyosis) and pregnancy are found in the literature. In most of the reports a diagnosis of a myomatous uterus was the indication for laparotomy. Five cases of uterine rupture during pregnancy were reported in the literature; endometriosis showed microscopically in sections through the areas of rupture. Uterine atony and post-partum hemorrhage in three cases were explained on the basis of internal endometriosis. The adenomyoma in two cases was a dystocia factor, indicating delivery by cesarean section. One ectopic pregnancy was found by Sampson in an area of cornual adenomyoma, after an attempted tubal sterilization. Internal endometriosis may or may not be a factor in the production of spontaneous abortions, miscarriages, and placenta previa. In the twelve cases of internal endometriosis and pregnancy where the ages were given, the average age was 36.1 years. Of ten of these cases, four were primigravidas.

6. External endometriosis complicating pregnancy is most common in the rectovaginal septum and ovarian regions.

7. Rectovaginal endometriosis, usually arising from the cul-de-sac of Douglas, may present symptoms mimicking threatened or inevitable abortion, and the accurate diagnosis and treatment depend upon speculum and pelvic examination, together with biopsy confirmation whenever possible. Eleven cases of this type of endometriosis and pregnancy were found in the literature. One case, 27 years old, married less than two years, had three children, all under one year of age after a series of complications. Rectovaginal endometriosis was frequently found to increase in size up to the fourth month of pregnancy and then regress in size until term.

8. Ovarian endometriosis and pregnancy were reported seven times in the literature. One case was ovarian endometriosis and an ovarian pregnancy in the same ovary. Rupture of an endometrial cyst is infrequent, and no case was found in the literature of this complication during pregnancy. Case 1, encountered in our clinic, was a 25-year-old primigravida who had an exploratory laparotomy and cesarean section, hysterectomy, bilateral salpingo-oophorectomy because of the rupture of one of two endometrial cysts in the thirty-sixth week of pregnancy. The rupture was the result of the tearing of the adherent cyst wall by the enlarging uterus. Case 2 was a 23-year-old female who had a large endometrial cyst of the right ovary and a small endometrial cyst of the left ovary encountered at a laparotomy when she was twelve

weeks pregnant with her first pregnancy. A right salpingo-oophorectomy, resection of the left ovarian cyst, and appendectomy were done, and she delivered in the thirty-fifth week of the pregnancy a 2,390 Gm. male child.

9. Two cases of cervical endometriosis, one of anterior cul-de-sac endometriosis, one of an inguinal endometrial cyst, one of small intestinal endometriosis with perforation and peritonitis, and two of abdominal scar endometriosis were found associated with pregnancy in the literature.

10. The average age, of twenty-five cases of external endometriosis and pregnancy, was 31.5 years. Of seventeen cases where the parity was given, six were pregnant for the first time.

11. A decidual reaction of the endometrial stroma in these cases of endometriosis and pregnancy was an almost constant finding, as would be expected.

12. Many cases of unrecognized endometriosis go through pregnancy and the puerperium without complication. The ways in which it may complicate pregnancy are discussed.

13. A plea is entered for conservative pelvic surgery whenever possible in cases of endometriosis, for they *can* and *do* become pregnant.

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CAUDAL ANALGESIA: AN EXPERIMENTAL AND ANATOMICAL STUDY*

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EDWARDS and Hingson,¹ to whom credit is properly given for introducing continuous caudal analgesia into the field of obstetrics, have proposed that "The fundamental knowledge of the anatomy of the sacral area . . . is a prerequisite for success in continuous caudal analgesia."²

Experimental and anatomical studies pertaining to the level of termination of the dural sac, to the size of the sacral hiatus, and to the disposition of solutions injected into the epidural space of the vertebral canal through the sacral hiatus have been reported. Farr,³ Shaw⁴ and Elliott⁵ injected fresh bodies a short time after death and noted the heights reached by varying amounts of solution. In addition to similar experiments Brenner⁶ noted the level of the termination of the dural sac as did Grodinsky and Best.⁷ Thompson⁸ tabulated his observations on a series of dissecting-room cadavers and noted as well the level of the apex of the hiatus. A search of the literature reveals that study of the anatomy of the sacral area relative to analgesic technique has not been pursued to any extent in the last decade except for the skeletal investigations of the sacrum made by Trotter and Letterman.^{9, 10} A question of significance in the problem of the technique of continuous caudal analgesia not yet answered is that of the distance between the level of termination of the dural sac and the apex of the hiatus.

This report is concerned with (1) the level in the epidural space to which a given amount of fluid injected through the sacral hiatus will pass, (2) a comparison of the size of the hiatus sacralis in the recent and skeletonized state, and especially (3) the distance between the caudal end of the dural sac and the apex of the hiatus sacralis.

Material and Methods

A series of 56 cadavers, 46 males and 10 females, comprised the material. The majority of these were prepared especially for this study; they were embalmed and then immersed in a tank of 3 per cent carbolic acid until two days before use. The exceptions are: nine which were used for routine class dissection and had been disarticulated between the third and fourth thoracic vertebrae; and one which had been dissected also and had been disarticulated between the fifth lumbar and first sacral when it reached us.

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The entire procedure was as follows:

1. A special malleable, $2\frac{1}{2}$ inch, 19 gauge needle with stylet¹¹ was inserted into the midline of the sacral hiatus as determined by palpation.
2. The skin, subcutaneous tissue, and muscles were reflected exposing the spinous processes and laminae of the presacral vertebrae. The ligamenta flava and other articular ligaments were undisturbed. The soft parts over the dorsum of the sacrum were left intact.
3. Thirty or sixty c.c. of a combined aqueous solution of a radio-opaque substance and a dye were injected (by the same person and as rapidly as the tissues permitted); lead acetate or lead nitrate was used for the former, a 5 per cent acid fuchsin for the latter.
4. In 12 of the cases the solution was introduced and followed under the fluoroscope.
5. In two-thirds of the cases the injection was made with the body prone; this position was maintained throughout the entire procedure. In the remaining one-third the injection was made with the body resting on the right side in a true lateral position after which it was immediately turned supine.
6. Fifteen minutes after the colored opaque solution had been introduced, the vertebral canal was exposed. Removal of the laminae and spinous processes was accomplished by parallel saw cuts made just medial to the articular processes. Observation of the disposition of the dye was made at this time.
7. The dorsum of the sacrum and especially its hiatus was now laid bare of the soft parts. Measurements were made of the hiatus: width of base, length, and anteroposterior diameter of the sacral canal at the apex of its hiatus. The level of the apex of the hiatus was marked on the ventral wall of the canal by insertion of an ordinary dress-maker's pin.
8. The dorsal wall of the sacral canal was removed usually in one piece after appropriate saw cuts. By this procedure the dural sac was exposed, examined, and its lower limit demarcated by insertion of another pin. The distance between the two pins on the anterior wall of the sacral canal was measured with a flexible steel tape.
9. The sacrum was skeletonized (after the method described by Terry¹²) and all the above measurements repeated on the cleaned bones.

Levels Reached by Solution

In forty-nine bodies injections of 30 c.c. of the combined solution were made uniformly into the epidural space through the hiatus of the sacral canal. Since two different positions were used for the bodies (33 prone, 16 lateral-to-supine) the results will be considered in two groups according to position. The dye reached the level of the foramen magnum twice as often when the body was prone as when it was in the true lateral and then turned supine. In five bodies in the prone position the dye did not get beyond the level of the sacrum whereas this result was not obtained in the other group. In both groups the distribution of the injected fluid was scattered at various levels between the sacrum and foramen magnum. In the prone position there appeared to be some concentration in the lumbar and lower thoracic region and in the lateral-to-supine position the dye reached the upper thoracic region in the majority of bodies. The vertebral levels attained infrequently or not at all were the upper thoracic for the prone

group and the cervical vertebrae for the lateral-to-supine group. A graphic representation of the levels reached by the solution in both groups is made in Fig. 1 (A and B) and a summary (in per cent) is given in Table I.

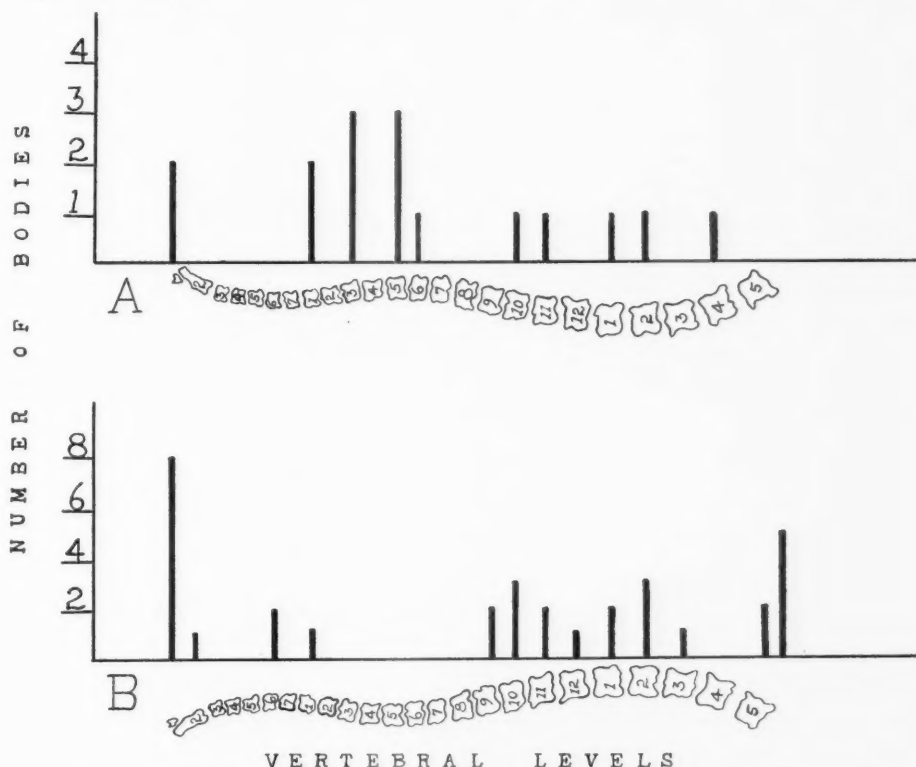


Fig. 1.—Levels reached by 30 c.c. of combined solution injected into the epidural space through the hiatus of the sacral canal. (The outlines of the column were taken from H. Virchow, *Anat. Anz., Ergänz. Heft 38, 1911.*)

A. Cadavers (16) were in a true lateral position and turned supine immediately after the injection.

B. Cadavers (33) were in the prone position.

Assuming that the vertebral bodies are equal units, it was determined that the mean reached by the solution in cadavers in the prone position was the seventh thoracic and in the lateral-to-supine position the fifth thoracic vertebra.

TABLE I. THE REGIONAL LEVELS (IN PER CENT) REACHED BY 30 C.C. OF SOLUTION INJECTED INTO THE EPIDURAL SPACE THROUGH THE HIATUS OF THE SACRAL CANAL ACCORDING TO POSITION OF THE CADAVER

LEVELS	PRONE	LATERAL-TO-SUPINE	BOTH	TOTAL NUMBER OF BODIES
Sacrum	15.2	0	10.2	5
Lumbar	24.2	18.8	22.5	11
Lower 6 thoracic	24.2	12.5	20.4	10
Upper 6 thoracic	3.0	56.2	20.4	10
Cervical	9.2	0	6.1	3
Foramen magnum	24.2	12.5	20.4	10
Total	100.0	100.0	100.0	49

The dye was deposited in the subarachnoid space in two cases. In one the distance between the apex of the hiatus and the lower limit of the dural sac was 58 mm., in the other 40 mm.; both distances are well within the overall length of the shaft of the malleable needle. In these bodies the dye was found in the epidural space as well and had reached the level of the foramen magnum.

In twelve bodies in the lateral-to-supine position the injection was made under the fluoroscope. The fluid traveled rapidly and reached its ultimate level in the epidural space immediately.

In three cadavers, all in the prone position, 60 c.c. of solution were injected: in one, the dye reached the level of the foramen magnum, in another it passed only to the level of the fifth lumbar vertebra and in the third the solution had had some gelatin added and was not found above the level of the tenth thoracic vertebra. In three more cadavers, again in the prone position, the solution extended all the way to the point where disarticulation had been made between the third and fourth thoracic vertebrae. One cadaver (the fifty-sixth) was not injected since it had been disarticulated between the fifth lumbar and first sacral vertebrae.

Size of Hiatus in the Recent and Skeletonized States

In the series of 56 bodies only 53 sacra could be used for measurement of the hiatus sacralis in the recent state. Two had complete agenesis of the dorsal wall; part of the bone had been eroded away by a decubitus in the remaining one, and finding the outline of the hiatus was impossible. During skeletonization the dorsal wall of the sacral canal of three specimens disintegrated to such an extent that measurements of the hiatus could not be repeated. Therefore, data are present for only 50 cleaned sacra.

A comparison of measurements made on the hiatus of the sacral canal in the recent state and of those made on the skeletonized sacra is summarized in Table II. There was no statistically significant difference between the means of any of the three pairs of measurements.

TABLE II. MEANS IN MM. (IN THE RECENT STATE AND AFTER SKELETONIZATION) OF WIDTH OF BASE OF HIATUS, OF LENGTH OF HIATUS AND OF ANTEROPOSTERIOR DIAMETER OF THE VERTEBRAL CANAL AT THE LEVEL OF THE APEX OF THE HIATUS

	IN THE RECENT STATE	AFTER SKELETONIZATION
Width of base	18.0 \pm 0.3	19.3 \pm 0.3
Length of hiatus	26.3 \pm 1.0	25.3 \pm 0.9
Anteroposterior diameter	5.8 \pm 0.2	6.1 \pm 0.2

The anteroposterior diameter of the vertebral canal at the level of the apex of the hiatus was three mm. or more in all cases. There was no difficulty in the procedure of insertion of the needle.

The mean level of the apex of the hiatus was found to be the lower third of the fourth sacral vertebral body. In 38.4 per cent of the cases the apex was at a level cephalad to the mean with the highest occurring at the joint between the second and third sacral vertebrae. (Fig. 2, broken lines.)

Distance Between Dural Sac and Apex of Hiatus Sacralis

The point of termination of the dural sac occurred between the levels of the middle of the first and the middle of the third sacral vertebral bodies. The mean point was the middle third of the body of the second sacral vertebra. Of the 56 sacra studied, the termination of the dura was at a level cephalad to the mean in 37.5 per cent and caudad in 46.4 per cent. In no case was there observed a partition, fenestrated or otherwise, extending between the dorsal surface of the dura and the dorsal wall of the vertebral canal. However, the dura in one of the two bodies in which the solution entered the subarachnoid space was quite tightly adherent to the dorsal bony wall of the canal in the sacrum.

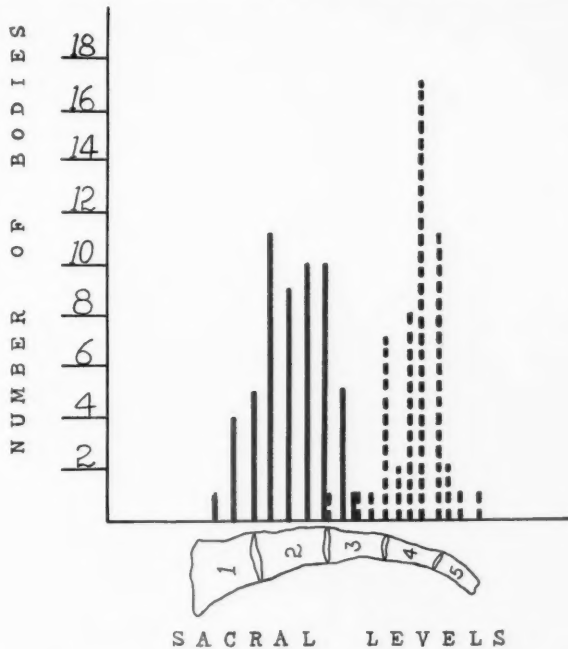


Fig. 2.—Levels of the inferior extent of the dural sac (solid lines) and of the apex of the hiatus of the sacral canal (broken lines).

The same 53 cases used in determining the size of the hiatus (in the recent state) afforded measurements of the distance between the apex of the hiatus and the termination of the dural sac before and after skeletonization. There was no significant difference between measurements made under these two conditions. The mean distance was 47.4 mm. on the cleaned bones with a range of 19 to 75 mm. A summary of the measurements is given in Table III.

Thus, it may be seen that there was 42 per cent of the cases with a shorter distance between the apex of the hiatus and the dural sac than the mean distance.

A diagrammatic representation of the inferior limit of the dural sac and of the superior limit of the apex of the hiatus is made in Fig. 2. A correlation between the level of the apex (the superior limit at which the needle might be passed into the sacral canal) and the distance from the apex to the dural sac was not obtained.

TABLE III. INCIDENCE OF THE DISTANCES BETWEEN THE APEX OF THE HIATUS AND THE LOWER EXTENT OF THE DURAL SAC; PERCENTAGE INCIDENCE OF THE MEAN AND OF THOSE DISTANCES SHORTER AND LONGER THAN THE MEAN

DISTANCE IN MM.	NUMBER OF BODIES	PER CENT
16 to 20	1	
21 to 25	1	
26 to 30	5	
31 to 35	5	42.0
36 to 40	3	
41 to 45	7	
46 to 50	12	22.0
51 to 55	5	
56 to 60	5	
61 to 65	2	36.0
66 to 70	3	
71 to 75	4	
Total	53	100.0

Discussion

The levels reached by a given amount of solution injected into the epidural space through the sacral hiatus of embalmed cadavers were found to vary throughout the extent of the column. Similar findings were obtained by Thompson⁸ and by Grodinsky and Best⁷ who have experimented on the embalmed cadaver. The reports on fresh bodies by Shaw,⁴ Farr³ and Elliott⁵ indicate that the levels reached were proportionate to the amount of solution injected. Brenner's report⁶ is the exception, if his material is correctly assumed to be embalmed cadavers; he found the level to be determined by the amount of solution injected. The results may be summarized as follows:

AUTHOR	DATE	NUMBER OF BODIES	STATE OF MATERIAL	POSITION	TIME OF INJECTION	AMOUNT INJECTED	LEVEL REACHED PROPORTIONATE TO AMOUNT?
Thompson	1917	30	Embalmed	?	?	30 c.c.	No
Brenner	1924	?	Embalmed?	?	?	20 to 120 c.c.	Yes
Shaw	1926	11	Fresh	?	5 min. after death	15 to 17 c.c.	Yes
Farr	1926	2	Fresh	"Lateral-horizontal"	12 hrs. after death	30 to 118 c.c.	Yes
Elliott	1926	8	Fresh	?	3 to 6 hrs. after death	30 to 120 c.c.	Yes
		1	Living	?		?	Yes
Grodinsky and Best	1929	12	Embalmed	Prone; 3 with head raised	?	30 to 100 c.c.	No
Present study	1944	52	Embalmed	36 prone 16 lateral-to-supine	More than 30 days after death	30 c.c.	No
		3	Embalmed	Prone	More than 30 days after death	60 c.c.	No

It would be of value to have reports on a larger series of fresh bodies and on the living for comparison with levels reached in the embalmed cadaver.

Farr³ states that "... the position in which the patient is placed during, or directly after, the injection may have some bearing on the results." It is suggested by these cadaver experiments that the position of the body at the time of injection may contribute to the determination of the level reached. In the prone position there was some tendency for the solution to travel no farther than the lumbar or lower thoracic region whereas in the lateral-to-supine position the dye tended to reach the upper thoracic region. However, the solution reached the level of the foramen magnum twice as frequently when the body was prone as when it was lateral and then turned supine. It is unfortunate that of all the investigators only Grodinsky and Best⁷ have considered different positions of the body. They placed all the cadavers prone and for three the head was raised; no differences resulting from the varied positions were pointed out. Observations of the solution under the fluoroscope showed that it traveled quickly and reached its superior level immediately. Thus, it would be accurate to consider the "lateral-to-supine" position as "lateral," for after the body was turned supine there was no apparent alteration in the height reached by the solution.

It was of interest that in the two bodies whose dura was punctured, the solution in the epidural space reached the level of the foramen magnum. The obvious explanation of the solution being deposited in both the subarachnoid and epidural spaces is supplied by the needle which has an opening not only at the tip but also in the wall close to the tip. Presumably the tip of the needle had just pierced the dura, whereas the opening in the wall of the needle allowed fluid to escape into the epidural space. This is evidence that an amount of solution smaller than 30 c.c. can easily travel to the level of the foramen magnum in the embalmed cadaver.

The mean measurements of the hiatus of the sacral canal were not significantly different before and after skeletonization. As might be expected the measurements taken on the sacra in the recent state are somewhat smaller than those taken after skeletonization excepting the one of the length of the hiatus. This may be explained by the fact that it is not always possible to determine on sacra in the recent state the exact level of the base of the hiatus. The strong, dense superficial posterior sacrococcygeal ligaments may simulate elongated sacral cornua and thus the level of the base of the hiatus can be interpreted to be too far caudad with the resultant increase in length; this was the condition in several cases of this series. The means of the skeletonized sacra are slightly greater than those reported by Trotter and Letterman^{9, 10} but the differences are expectedly insignificant since the source of the material and the method of preparation were the same for both

studies. The mean level of the apex is at the lower third of the fourth sacral body but in 38.4 per cent of the series it lies at a level cephalad to this plane. If the needle should be inserted at the apex there is increased danger of puncturing the dural sac. Earlier reports^{9, 10} have presented even higher percentages.

The inferior extent of the dural sac is generally described as occurring at the level of the second sacral vertebra.¹³⁻¹⁶ In this series of cadavers the mean level was at the middle third of the second sacral vertebra. Brenner⁶ examined the termination of the dural sac but did not tabulate his results or state the number of sacra examined. Thompson⁸ listed the level of termination in 14 cases; of these, three were between the bodies of the second and third sacral vertebrae and four at the level of the body of the third sacral vertebra. In the 12 cadavers examined by Grodinsky and Best⁷ the dural sac ended at the level of either the first or second sacral vertebra. In the 56 cases of the present study the termination of the dural sac was caudad to the level of the body of the second sacral vertebra in 28.6 per cent or 16 cases. However, the level of the termination of the dural sac is significant in the administration of continuous caudal analgesia chiefly in its proximity to the level of the apex of the hiatus of the sacral canal. Since the apex of the hiatus was found to be cephalad to the mean (lower third of fourth sacral body) in more than one-third of the cadavers and the dural sac extended caudad to the mean (middle third of second sacral body) in almost one-half of the series, the distance between the two was very much reduced over that classically described.

The mean distance between the apex of the hiatus sacralis and the termination of the dural sac was 47.4 mm. Two different lengths of needles are recommended for use clinically, a 3 inch (76 mm.) and a 2½ inch (63 mm.) needle. If allowance of 10 mm., which may be considered average, is made for skin and subcutaneous tissue there is left a 66 mm. or 53 mm. length of needle to lie in the canal. The distance between the apex and the dural sac was less than 66 mm. in 86.8 per cent or 46 of the 53 cases and less than 53 mm. in at least 64.2 per cent or 34 cases. From this the importance is seen of the step in the procedure which instructs one to depress the hub of the needle after its tip enters the canal but before the full length of its shaft is driven in. Thus, the point is elevated so that it may approximate the dorsal wall of the sacral canal and thereby avoid the dura which is adherent to the ventral but usually free from the dorsal wall.

Summary

1. Experimental and anatomical studies pertaining to continuous caudal analgesia were carried out on 56 embalmed cadavers.
2. Levels reached by a constant amount of combined solution injected into the epidural space through the hiatus of the sacral canal varied throughout the extent of the column. These results compared

favorably with the results of others who have utilized embalmed cadavers but did not agree with the findings obtained by workers who injected fresh cadavers.

3. Measurements of the dimensions of the hiatus canalis sacralis were not significantly different before and after skeletonization.

4. The mean level of the apex of the hiatus was found to be the lower third of the body of the fourth sacral vertebra. In 38.4 per cent the level was cephalad to the mean.

5. The mean level of the termination of the dural sac was the middle third of the body of the second sacral vertebra; in 46.4 per cent of the bodies examined it extended caudad to this level.

6. The mean distance between the apex of the hiatus canalis sacralis and the inferior extent of the dural sac was 47.4 mm.; in 42 per cent of the cases the distance was less than the mean. In 86.8 per cent the lower limit of the dura could have been reached by the 3 inch needle; in 64.2 per cent by the 2½ inch needle (after allowing 10 mm. for skin and subcutaneous tissue).

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THE TREATMENT OF PROTHROMBINOPENIA WITH A WATER-SOLUBLE MENADIONE

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POTENTIAL danger of hemorrhage in the newborn infant has long been recognized but determination of its cause has until recently baffled investigations.

Quick and Grossman¹ reported that, with recognition of prothrombin deficiency as a cause of hemorrhage and discovery that vitamin K is essential for synthesis of prothrombin, came a new approach to study and control of hemorrhagic disease of the newborn infant.

Quantitative determination of blood prothrombin in newborn infants by Quick's method shows that, at birth, blood prothrombin is relatively high, about 60 to 75 per cent of the normal adult value. Soon after birth, however, blood prothrombin decreases sometimes to a very low level. Prothrombin is lowest on the first day, higher during the second and returns to normal after the third day. Many of our cases, as shown by the charts, did not return to normal until after the fifth or seventh day. All the cases, however, with appropriate treatment returned to normal by time of discharge on the tenth day.

Prothrombinopenia may occur with or without jaundice and with or without bleeding. There is no definite relationship between the degree or duration of icterus and prothrombin deficiency. However, prothrombin levels approaching dangerous conditions are encountered most frequently in jaundiced patients.

When the prothrombin time was above 18 seconds in our series (Quick method) the infants invariably became jaundiced on the third day. In former years the explanation of this onset of icterus was that it was purely hemolytic, a result of the reduction of the polycythemia of the fetus with the production of bilirubin more rapidly than the liver is able to excrete it. However, Salmon and Richman² state that, if this is the only factor, there should be some demonstrable relationship between the degree of blood destruction and the degree of hyperbilirubinemia. Not all investigators have found this to be true.

Investigations of changes in the erythrocyte fragility seen during the neonatal period have shown results to be at variance.

Physiologic icterus of the newborn infant, in so far as is known, in no way impairs the health or well-being of the infant and is seen so frequently as to be looked upon as a normal occurrence. However, this

finding has been the subject of considerable investigation, not so much for its own importance, as for the possibility that it might reflect certain other important physiologic changes of the neonatal period.

Whatever the significance may be, we found that a great many infants developed icterus on the seventh day whose mothers gave a history of having had either gallbladder disease, diarrhea or colitis. This may give us a clue as to what method of treatment should be followed before the mother is delivered and what to expect in the way of newborn phenomena.

Adoption of early diagnostic laboratory methods at the time of delivery will, in many cases, reward the vigilant obstetrician. Indeed, such procedures instituted at our hospital during this study more than doubly rewarded the staff members in seeing many of their cases saved from certain death.

Ross and Malloy,³ Russell and Page,⁴ McCreedy, et al.⁵ report excellent results with the use of vitamin K in raising the prothrombin levels and decreasing the incidence of spontaneous hemorrhage in their series.

Fitzgerald and Webster⁶ have found that the normal depression of the prothrombin level, which occurs from the second to the fifth day after birth, is much greater when barbiturate analgesics are used during labor. They believe that administration of vitamin K to the mother during labor will prevent this further depression and lower the incidence of hemorrhage of the newborn infant, and that vitamin K should, therefore, be given when barbiturate analgesics are used.

Finally, Clifford et al.⁷ recommended that vitamin K be universally used to prevent the hypoprothrombinemia of the newborn and thereby protect the infant during any possible period of trauma, asphyxia, sepsis or other hazards. They favor administration of vitamin K to the mother, although they state that "to provide every possible protection in the light of our present knowledge and experience, every newborn baby could well be given vitamin K at birth whether or not there has been previous maternal administration."

One of our aims in making this study was to determine the value of a synthetic vitamin K, without the administration of bile, for obviously we could not give the newborn infant any medicinal bile. It had to be of necessity a water-soluble (injectable) vitamin K, or "menadione," in ampoule form to be given by intramuscular injection. Then a tablet without medicinal bile to the mother.

The results of our investigations are herein presented. The period of observation ran for six months, August, 1943, through January, 1944.

Clinical Material

Maternity patients admitted to the Menorah Pavilion of the Beth-El Hospital, and their infants in the nurseries. The patients were both private and service. They were predominately primiparas. The birth weight and weight curve did not differ from the average. The majority were artificially fed.

A suitable water-soluble menadione preparation was sought and several were chosen with which to start this series. It was found, however, upon investigation, that these water-soluble preparations were of different strengths. Harrow⁸ states that all of these synthetic vitamin K active preparations have greater potency than natural vitamin K and, of these, menadione is the most potent. On a basis of standard units per milligram, menadione rates 1,000 standard units while natural vitamin K rates 300 standard units. Ranking in potency between these two substances, there were several synthetic vitamin K active preparations but none of them were as potent as menadione. Menadione, itself, is oil-soluble and can only be administered effectively in cases of biliary deficiency and obstructive jaundice with the supplementary administration of bile salts. Further, oil solutions are more slowly absorbed by the tissues than a water-soluble preparation. It was found, however, that several preparations of water-soluble menadione were either being marketed or in a state of clinical experimentation and it was decided to try several of these in the following tests.

Because most of these substances produced irritation and pain after injection, only one of these was retained. This was an aqueous solution of menadione and sodium salicylate to which metycaine (Lilly) had been added. This product* contained one milligram of menadione per c.c. (1,000 standard units vitamin K activity) and was also available in tablet form, each tablet containing $\frac{1}{2}$ milligram of menadione (500 standard units vitamin K activity).

Methods

The blood specimens were taken, at the time of delivery, from both the mother and the infant. The fortuitous coincidence that a quantitative method for determining prothrombin was developed, almost simultaneously with discovery of vitamin K, gave impetus to study of blood coagulation. These studies have solved the problem of controlling certain types of hemorrhage and have given a rational explanation to the blood clotting mechanism. The simplest concept of coagulation was proposed by Morawitz. According to his theory, which is now widely accepted, prothrombin, thromboplastin and calcium interact to form thrombin and this latter agent reacts with the fibrinogen of the blood, changing it to fibrin.

Thus, only four substances are required for coagulation. Since calcium and fibrinogen are very rarely responsible for any demonstrable change in the coagulation process, only prothrombin and thromboplastin remain as factors potentially instrumental in causing disturbance in blood clotting.

Prothrombin occurs only in plasma and is closely associated with the proteins. Thromboplastin is widely distributed in the body, but is intracellular and becomes available only when the cells are ruptured. The amount of prothrombin available, in the blood, to play a part in coagulation, is diminished in the absence of vitamin K.

Quantitative determination of blood prothrombin is indispensable as a guide to therapy of prothrombopenic hemorrhage. Our laboratory used a slight modification of Quick's method. We used 4.5 c.c. of fresh venous blood with 0.5 c.c. of sodium oxalate. This was centrifuged. Then 0.1 c.c. of the plasma was mixed with 0.1 c.c. of thromboplastin

*Aquione, supplied by Ernst Bischoff Company, Inc., Ivoryton, Conn.

TABLE I. PATIENTS DID NOT RECEIVE ANY VITAMIN K ON ADMISSION (CONTROLS)

CASE NO.	PATIENT	PROTHROMBIN TIME (SEC.)	TIME LABOR	REMARKS
1.	J. K. Para o, grav. i, age 24	18	38' 55"	Manual rotation and midforceps delivery of a living female child. Patient developed post-partum psychoses.
2.	H. F. Para o, grav. i, age 21	24	3' 10"	Spontaneous delivery of a living male child.
3.	H. S. Para o, grav. i, age 19	20	23' 20"	Low forceps delivery of a living male child.
4.	C. G. Para o, grav. i, age 24	19	2' 55"	Spontaneous delivery of a living male child. Mother a cardiac.
5.	E. G.	26	10' 10"	Spontaneous delivery of a living female child.
6.	H. B.	21	4' 57"	Spontaneous delivery of a living male child. Baby became slightly jaundiced on the seventh day.
7.	C. T.	25	28' 45"	Low forceps delivery of a living child.
8.	L. R.	25	8' 30"	Low forceps delivery of a living child.
9.	J. A. Para o, grav. i, age 22	18	13' 45"	Low forceps delivery of a living female child.
10.	S. W. Para o, grav. i, age 28	24	10' 30"	Low forceps delivery of a living female child.
11.	K.	26	17' 5"	Spontaneous delivery of a living child.
12.	J. P. Age 29	30	13' 58"	Low forceps delivery of a living immature female Mongoloid. Weight 4 pounds 14 ounces. Height 18 inches.
13.	A. M.	24	7' 10"	Spontaneous delivery of a living female child.
14.	R. F.	28	12' 45"	Spontaneous delivery of a living female child.
15.	S. G.	29	5' 59"	Spontaneous delivery of a living female child.
16.	A. S.	25	8' 16"	Spontaneous delivery of a living male.
17.	J. K.	25	30' 15"	Spontaneous delivery of a living female.
18.	H. L.	35	14'	Spontaneous delivery of a living male.
19.	H. M.	18	22' 48"	Low forceps—living child.
20.	E. R.	24	15' 20"	Spontaneous delivery of a living male.
21.	F. S.	27	8' 9"	Spontaneous delivery of a living male.
22.	G.	36	10' 41"	Spontaneous delivery—male. (Baby expired.) Born Oct. 13, readmitted on Nov. 12, died Nov. 12, 1943. Diagnosis: Bronchopneumonia, dehydration.

and quickly added 0.1 c.c. of calcium chloride and watched for the beginning of the clot. Normal is between 10 to 13 seconds. The control was blood from a normal (nonjaundiced) person.

All solutions must be tested before each test and the thromboplastin must always be in ice or kept at freezing temperature. The time from the addition of calcium to the formation of a clot is recorded with a stop watch.

TABLE II. NEWBORN INFANTS OF MOTHERS WHO DID NOT RECEIVE MENADIONE† (CONTROLS)

BABY	MOTHER'S PRO- THROMBIN TIME (SEC.)	CORD PRO- THROMBIN TIME (SEC.)	1ST DAY PRO. (SEC.)	3RD DAY PRO. (SEC.)	5TH DAY PRO. (SEC.)	7TH DAY PRO. (SEC.)	REMARKS
K.	18	20	28	30	21	17	Slight jaundice.
F.	24	18	18	23	19	19	Icteric tinge.
S.	20	22	41	55*	20*	14	Marked jaundice 3rd day.
G.	19	19	18	34	38*	26	Slight jaundice.
G.	26	27	38*	18	20	18	Skin clear.
B.	21	19	15	20		35	Jaundiced, 7th day.
T.	25		21	26	18		Skin clear.
R.	25	53	53*	38*	30*	24	Moderate jaundice.
A.	18		19	18	25	24	Clear.
W.	24	17	18	21	20	18	Clear.
K.	26		20	20	30	27	Slight icteric tinge.
P.	30	27	20	23	33*	23	Infant died, 9th day.
M.	24		20	22	32	22	Clear.
F.	28		28	67* (2)	38*	18	Moderate jaundice.
G.	29		35	27*	23	20	
S.	25	28	21	24	34*	22	Skin clear.
K.	25	21	27	30*	22	24	Slight icteric tinge.
L.	35	24		25	38	22	Skin clear.
M.	18	19	18	18	18		Skin clear.
R.	24	18	20	30*	27	23	Slight jaundice.
S.	27	23	30	24	35	26	Skin clear.
G.	36	55		62*	58*	38*	Marked jaundice.

(Aquinone injection started on fifth day. Other water-soluble preparation used previously.)

*Ampoules aquinone (menadione) administered to infant after birth for the safety of the newborn.

†Detailed list of the newborn infants from mothers in Table II who didn't receive vitamin K. Vitamin K by ampoule was given only when the prothrombin was prolonged, $\frac{1}{2}$ c.c. in each arm intramuscularly.

In Table V, including mothers and newborn infants, we attempted to determine what significance previous history of either gall-bladder disease, colitis, diarrhea, or prolonged medication had on the prothrombin time. We also took blood smears on all the newborn infants. This point occurred to us after the loss of Case 6 (Table III). Surprisingly we picked up a case (13), a woman, 31 years of age, who had

TABLE III. CASES GIVEN ONE TABLET MENADIONE TREATMENT BY MOUTH AFTER ONSET OF LABOR—ON HOSPITAL ADMISSION

CASE NO.	PATIENT	MOTHER'S PRO-THROMBIN TIME (SEC.)	CORD PRO-THROMBIN TIME (SEC.)	TIME LABOR	REMARKS
1.	G. V. Para i, grav. ii, age 28	14		25' 25"	Low forceps delivery of a living male child. Prenatal period normal.
2.	T. C. Para i, grav. ii age 29	16		5' 43"	Low forceps delivery of a living female child. Prenatal period normal.
3.	R. F. Para i, grav. ii, age 28	15		4' 10"	Spontaneous delivery of a living female child.
4.	J. V. Para i, grav. ii, age 29	17		3' 15"	Spontaneous delivery of a living female child.
5.	M. H. Para ii, grav. iii, age 25	17		3' 48"	Spontaneous delivery of a living male child.
6.	L. S. Para o, grav. i, age 24	65	87	6' 5"	Manual rotation and midforceps delivery of a living male child. Infant had congenital atelectasis and erythroblastosis at birth. Baby expired within a few hours.
7.	H. O. Para i, grav. ii, age 25	15		20' 40"	Spontaneous delivery of a living male child.
8.	S. G. Para i, grav. ii, age 21	18		10' 15"	Low forceps delivery of a living female child.
9.	M. M. Para i, grav. iii, age 34 Premature due October 9th	46	66	13' 5"	History of one stillborn and one miscarriage. Bleeding on admission. Tabs. II of aquinone given. Spontaneous delivery of a living premature—male. Weight 3 pounds 6 ounces.
10.	A. L. Para i, grav. iii, age 31	17		4' 55"	Spontaneous delivery of a living female child.
11.	A. L. Para o, grav. i, age 20	15		11' 20"	Spontaneous delivery of a living male child.
12.	B. H. Para i, grav. ii, age 26	13		6' 37"	Spontaneous delivery of a living female child.
13.	Y. P. Para i, grav. ii, age 21	16		7' 40"	Spontaneous delivery of a living female child.
14.	R. S.	16		12' 58"	Spontaneous delivery of a living child.
15.	M. H.	17		8' 40"	Low forceps delivery of a living child.
16.	M. F.	17		13' 40"	Low forceps delivery of a living child.

TABLE III—CONT'D

CASE NO.	PATIENT	MOTHER'S PRO-THROMBIN TIME (SEC.)	CORD PRO-THROMBIN TIME (SEC.)	TIME LABOR	REMARKS
17.	D. K.	13			Spontaneous delivery of a living child.
18.	T. B.	15			Low forceps delivery of a living child.
19.	M. S.	16			Spontaneous delivery of a living child.
20.	S. B.	14			Low forceps delivery of a living child.
21.	B. W.	20			Low forceps delivery of a living child.
22.	B. La R.	16			Low forceps delivery of a living child.
23.	M.	14			Low forceps. Male.
24.	F. K.	13			Male.
25.	F. R.	14			Male.
26.	N. F.	24			Born Oct. 6, expired Oct. 9. Diagnosis: Diarrhea of the newborn. Female.
27.	E. S.	15			Male.
28.	E. F.	15			Female.
29.	I. B.	16			Female.
30.	A. P.	18			Baby premature.
31.	A. C.	13			Living male child.
32.	S. S.	14			Living male child.
33.	R. L.	13			Living child.
34.	R. S. II.	16			Living child.
35.	E. E.	15			Living female child.

Note: In Table III all cases with exception of cases 6 and 9 showed a prothrombin time within normal limitations.

Case 6: The high prothrombin time of both mother and infant was a clue to hemorrhagic disease in the newborn. Infant died within a few hours of delivery. Diagnosis of erythroblastosis was made on smear taken at time of delivery, and marked secondary anemia, R.B.C. below 2 million.

Case 9: Premature was given adequate doses of vitamin K and was discharged in good condition when infant weighed approximately six pounds.

a cholecystectomy done. Her infant was born in a pool of yellow stained amniotic fluid; blood smear only 2 nucleated cells; expired 16 hours after delivery; prothrombin time 30 seconds. This was a private case and no treatment was given.

Contrast this record with Case 10, male newborn infant with 58 seconds prothrombin. Smear showed 60 nucleated cells. This infant had immediate synthetic vitamin K therapy and made an uneventful recovery. The same result was obtained in Case 18. Here, too, a high prothrombin time was found. Adequate doses of synthetic vitamin K brought the prothrombin down to within normal limits.

Although the original intention of the authors was to follow through the value of synthetic vitamin K without the use of bile salts on both the mother and the infant, the project developed into determining a technique in the early diagnosis of erythroblastosis as a side issue. Several cases showed unusual high prothrombin time and a few had a concomitant increase in nucleated cells. One such case showed as high

TABLE IV. CASES HAD MENADIONE, BLOOD TAKEN FROM MATERNAL SIDE OF CORD AND BABY'S SIDE

CASE NO.	PATIENT	PROTHROMBIN TIME (SEC.)	REMARKS
1.	F. L.	15	Spontaneous delivery.
	Baby L.	20	Slight jaundice on 7th day.
2.	R. R.	16	
	Baby R.	22	Slight jaundice on 7th day.
3.	L. P.	13	
	Baby P.	18	Skin clear.
4.	M. F.	15	
	Baby F.	19	Skin clear.
5.	S.	15	
	Baby S.	19	Readmitted to children's pavilion. Died 10 days after discharge from hospital. Diagnosis: Diarrhea of newborn. Bronchopneumonia.
6.	G.	14	
	Baby G.	17	Skin clear.
7.	W.	13	
	Baby W.	18	Skin clear.
8.	P.	15	
	Baby P.	19	Slight jaundice.
9.	S.	15	
	Baby S.	17	Skin clear.
10.	G.	14	
	Baby G.	21	Slight icteric tinge.
11.	P.	13	
	Baby P.	16	Skin clear.
12.	M. R.	14	
	Baby R.	19	Slightly icteric.
13.	B. B.	16	
	Baby B.	18	Skin clear.

as 3:1 nucleated cells to white cells. This case (Golub) is herein given in detail. We are convinced that the early diagnosis, the transfusion of Rh negative blood, and giving synthetic vitamin K within three hours after diagnosis, were instrumental in saving the life of the newborn infant.

Recently, we discovered another case at the Brooklyn Women's Hospital, a 1-day-old infant (Belkin). Blood count: R.B.C. 1,500,000; nucleated cells 218 to 100 white cells, which after several transfusions of Rh negative blood and aquinone, then showed 3,500,000 R.B.C. and 2 per cent nucleated cells. The transfusion, plus daily intramuscular injections of vitamin K, turned the tide in this newborn infant.

Case History

Baby G. (female), birth weight, 7 pounds 11 ounces.

October 27, 1943.—The baby was admitted to the nursery, markedly jaundiced and showed some cyanosis around the lips. Within two hours after admission a blood smear showed 300 nucleated red cells to 100 white cells.

TABLE V. LATER SERIES OF CASES WITH PARTICULAR REFERENCE TO PREVIOUS HISTORY OF CHRONIC ILLNESS OR MEDICATION

DATE	NAME, AGE AND PARA OF PATIENT	HISTORY OF GALL-BLADDER DISEASE, ULCERATIVE COLITIS PROLONGED INTAKE OF MEDICATIONS		VITAMIN K QUANTITY AND WHEN	PRO- THROMBIN TAKEN	BLOOD SMEAR TAKEN	RESULTS		CLINICAL REMARKS
							MOTHERS' PRO- THROMBIN	CORD PRO- THROMBIN	
11/25/43 1.	M. A. Age 24 Para 0, grav. i	Negative. Took treatment for lues at one time.		6 A.M. 1 tablet	10 A.M.	2 nucleated red cells	Q. M.— 15 sec. Normal— 11 sec.	Q. M.— 19 sec. Normal— 11 sec. (male)	Spontaneous delivery.
11/26/43 2.	B. Age 27 Para 0, grav. i	Negative		4:45 P.M. 1 tablet	7:40 P.M.	2 nucleated cells	Q. M.— 14 sec. Normal— 12 sec.	Q. M.— 17 sec. Normal— 12 sec. (male)	Low forceps.
11/29/43 3.	R. Age 20 Para 0, grav. i	Negative		3:30 A.M. 1 tablet	8:20 A.M.	6 nucleated cells	Q. M.— 13 sec. Normal— 12 sec.	Q. M.— 18 sec. Normal— 12 sec. (female)	Spontaneous frank breech.
11/30/43 4.	R. Age 31 Para 0	Negative		1:30 A.M. 1 tablet	5:05 P.M.	None taken	Q. M.— 14 sec. Normal— 10 sec.	Q. M.— 18 sec. Normal— 10 sec. (female)	Spontaneous delivery.
11/30/43 5.	G. Age 29 Para 0, grav. i	Negative		8:15 P.M. 1 tablet	4 A.M. 12/1/43	Normal	Q. M.— 14 sec. Normal— 13 sec.	Q. M.— 20 sec. Normal— 13 sec. (male)	Low forceps. Baby jaun- diced on 7th day.
11/30/43 6.	F. Age 29 Para i, grav. ii	Negative		4:18 P.M. 1 tablet	6 P.M.	Normal	Q. M.— 14 sec. Normal— 10 sec.	Q. M.— 18 sec. Normal— 10 sec.	Spontaneous delivery. Baby jaundiced on 8th day.

12/ 1/43 7.	F. Age 31 Para 0, grav. i	Negative	12:15 A.M. 1 tablet	4:20 A.M.	1 nucleated cell	Q. M.— 16 sec. Normal— 12 sec.	Q. M.— 19 sec. Normal— 12 sec. (female)	Spontaneous delivery.
11/29/43 8.	A. Age 26 Para 0, grav. i	Spastic colitis	9:15 A.M. 1 tablet	11:40 A.M.	1 nucleated cell	Q. M.— 16 sec. Normal— 12 sec.	Q. M.— 19 sec. Normal— 12 sec. (male)	Low forceps.
12/ 2/43 9.	R. Age 36 Para i, grav. ii	Negative	12:28 A.M. 1 tablet	1:40 A.M.	3 nucleated cells	Q. M.— 12 sec. Normal— 10 sec.	Q. M.— 17 sec. Normal— 10 sec. (female)	Spontaneous delivery.
12/ 3/43 10.	F. Age 23 Para 0, grav. i	Negative	4:15 A.M. 1 tablet	11:55 A.M.	60 nucleated cells Hemoglobin 150%		Q. M.— 58 sec. Normal— 11 sec. (male)	Spontaneous delivery.
12/ 2/43 11.	T. Age 25 Para 0, grav. i	Negative	8 A.M. 1 tablet	9:15 A.M.	8 nucleated cells	Q. M.— 15 sec. Normal— 10 sec.	Q. M.— 22 sec. Normal— 10 sec. (female)	Spontaneous. Baby jaundiced on 7th day.
12/19/43 12.	M. Age 18 Para 0, grav. i	Negative	2:45 P.M. 1 tablet		Normal	Q. M.— 14 sec. Normal— 11 sec.	Q. M.— 17 sec. Normal— (female)	Spontaneous delivery.
12/ 7/43 13.	F. Age 31 Para ii, grav. iv	Cholecystectomy	10:30 A.M. 1 tablet	12:50 P.M.	2 nucleated cells	Q. M.— 28 sec. Normal— 12 sec.	Q. M.— 30 sec. Normal— 12 sec. (male)	Spontaneous delivery. Full of yellowish am- niotic fluid.
<i>Remark:</i> Newborn (Baby F.) was cyanotic and large amount of yellowish stained mucus was aspirated from baby. There was no pres- sure on fetal head during birth. Baby expired 16 hours after birth.								
12/ 9/43 14.	R. Age 29 Para i, grav. ii	Negative	10:30 A.M. 1 tablet		2 nucleated cells	Q. M.— 13 sec. Normal— 11 sec.	Q. M.— 17 sec. Normal— 11 sec. (male)	Spontaneous delivery.

TABLE V—Cont'd

DATE	NAME, AGE AND PARA OF PATIENT	HISTORY OF GALL-BLADDER DISEASE, ULCERATIVE COLITIS PROLONGED INTAKE OF MEDICATIONS	VITAMIN K QUANTITY AND WHEN	PRO- THROMBIN TAKEN	BLOOD SMEAR TAKEN	RESULTS MOTHERS' PRO- THROMBIN	RESULTS CORD PRO- THROMBIN	CLINICAL REMARKS
12/ 9/43 15.	S. Age 25 Para ii, grav. iii	Negative	10 A.M. 1 tablet		1 nucleated cell	Q. M.— 15 sec. Normal— 11 sec.	Q. M.— 18 sec. Normal— 11 sec. (male)	Spontaneous delivery.
12/10/43 16.	G. Age 32 Para i, grav. ii	Negative	8:30 A.M. 1 tablet		6 nucleated cells	Q. M.— 16 sec. Normal— 12 sec.	Q. M.— 20 sec. Normal— 12 sec. (male)	Spontaneous delivery.
12/14/43 17.	R. F. Age 22 Para i, grav. ii	Negative	8 P.M. 1 tablet		1 nucleated cell	Q. M.— 15 sec. Normal— 13 sec.	Q. M.— 19 sec. Normal— 13 sec. (female)	Spontaneous delivery.
12/23/43 18.	M. Age 20 Para i, grav. ii	Negative	4:30 A.M. 1 tablet		6 nucleated cells	Q. M.— 48 sec. Normal— 13 sec.	Q. M.— 65 sec. Normal— 13 sec. (male)	Spontaneous delivery.
12/24/43 19.	W. Age 30 Para ii, grav. iii	Negative	11:35 P.M. 1 tablet		3 nucleated cells	Q. M.— 19 sec. Normal— 13 sec.	Q. M.— 22 sec. Normal— 13 sec. (female)	Low forceps.
12/28/43 20.	M. Age 22 Para o, grav. i	Negative	7:05 A.M. 1 tablet		3 nucleated cells	Q. M.— 25 sec. Normal— 11 sec.	Q. M.— 28 sec. Normal— 11 sec. (female)	Spontaneous delivery.

Transfusion was ordered and given within two hours of admission, 60 c.c. of Rh negative blood into the scalp vein. Prothrombin time was 72 seconds Quick method, normal 12 seconds.

October 28, 1943.—Cyanosis and airhunger still present. Marked icterus to the skin, sclera and fingerbeds. Prothrombin time was 120 seconds Quick method, normal 13 seconds.

October 29, 1943.—Complete blood count and smear taken—showed as follows:

15.4 Gm. = 100% hemoglobin	Macrocytosis	3+
R.B.C. 2,500,000	Microcytosis	1+
W.B.C. 54,000	Polychromasia	3+
150 nucleated R.B.C.	Target cells	2+

October 29, 1943.—Child was given another transfusion, 60 c.c. Rh negative blood.

October 30, 1943.—Sixty-five cubic centimeters Rh citrated Rh negative blood again given into scalp vein. Prothrombin time 54 seconds Quick method, normal 12 seconds.

November 1, 1943.—Complete blood count showed: 10.5 = 68% hemoglobin, R.B.C. 3,500,000, 8 nucleated and W.B.C. 9,000.

There was a marked improvement noted in the child's general condition. Icterus clearing. Child was given still another blood transfusion of 60 c.c. Rh negative blood into a scalp vein. Prothrombin time 29 seconds Quick method, normal 12 seconds.

November 3, 1943.—Prothrombin time 19 seconds Quick method, normal 13 seconds. Normal reactions: Takes its feedings very well. Skin clear. Vitamin K (synthetic) given, twice daily during its stay in the hospital. Aqueous 1,000 units per dose (ampoule form) $\frac{1}{2}$ c.c. injected into each arm.

November 4, 1943.—Blood of baby was Rh negative.

November 8, 1943.—On discharge baby's weight was 8 pounds 13 ounces, no icterus, blood was Rh negative. Final blood count was as follows: 12 Gm. = 78% hemoglobin, R.B.C. 3,580,000, 2 nucleated, and W.B.C. 10,500.

Final Note.—Infant at home and is doing well.

Conclusions

1. Procedure for taking prothrombin time, smear and red blood count at time of delivery is recommended as a safeguard to forestall hemorrhagic disease of the newborn infant and early diagnosis of erythroblastosis fetalis.

2. Administration of water-soluble menadione in tablet or ampoule form without bile salts proves satisfactory even in obstructive jaundice. These cases will be reported in another paper now in preparation.

3. We have found that intramuscular injections work more rapidly than tablets. In cases of excessive bleeding before delivery, synthetic vitamin K clots the blood after a few hours.

4. Infants with hemorrhagic disease showed marked prolonged prothrombin time. A cord blood at birth shows a normal prothrombin time and a hypoprothrombinemia in the first three days of life. The hypoprothrombinemia and associated hemorrhages in the newborn infant were effectively prevented by the administration of $\frac{1}{2}$ milligram water-

soluble menadione tablet to the mother, 48, 4 hours before delivery. Infants delivered from mothers without menadione are adequately protected by intramuscular injections of 1 milligram (1,000 units) within 12 hours of delivery.

5. No toxic effects noted from aquinone tablets or ampoules. There is no evidence of tissue damage in the intramuscular injection of the ampoule and it was found that the water-soluble preparation is more quickly absorbed than menadione in oil solution. This insures a more rapid response to the medication. The mothers reported a sense of smartness in the area of the injection for about five minutes and then the irritation disappears, and it is markedly less than injection of any other soluble synthetic, of which the patient really feels considerable amount of pain for at least 24 to 36 hours. There is a slight induration of the tissue which eventually disappears without any untoward effects.

6. Premature infants show a moderately prolonged prothrombin time. One of our premature infants, suffering from asphyxia, showed marked prolongation of the prothrombin time. One milligram injected intramuscularly showed a rapid rise of the prothrombin time in eight days. One premature, a bleeder, given one milligram intramuscularly, controlled the spontaneous bleeding.

7. Intramuscular injections of 1 milligram (1,000 units) cause a rapid rise of the plasma prothrombin level of newborn infants with hypoprothrombinemia whether there is hemorrhagic tendency or no clinical manifestation of the depressed prothrombin level.

The therapeutic value of water-soluble menadione is established in hypoprothrombinemia and potential or actual hemorrhage of obstructive jaundice and the hemorrhagic diathesis of the newborn infant.⁹ It is not indicated in the various hemophilic or menorrhagic purpuras.

Hypoprothrombinemia and associated hemorrhage in the newborn infant are effectively prevented by daily oral administration to the mother during her last few weeks in pregnancy. To insure adequate protection for the infant, vitamin K, or its synthetic equivalent, should be given promptly after birth and for several days thereafter. Bleeding in hemorrhagic disease of the newborn infant is controlled within eight hours. Intramuscular injections are preferable. No toxic effects from any large doses have ever been noted.

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A STUDY OF THE USE OF DIETHYLSTILBESTROL IN INHIBITION AND SUPPRESSION OF LACTATION

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HORMONAL therapy has gained progressively wider clinical application in the past decade. In recent years such therapy has been placed on a more creditable and rational basis through the efforts of numerous workers in both experimental and clinical investigation. New fields of usefulness of endocrine therapy are being developed; and one of these is the employment of estrogens, natural and synthetic, for inhibition and suppression of lactation in puerperal women.

At the New York Lying-in Hospital, for the past ten years the routine generally adopted for the inhibition and suppression of lactation has been as follows: A tight binder is applied to the breasts and ice bags and sedatives are used to alleviate pain; fluids are restricted to 1,500 c.c. for three to four days and daily saline catharsis is urged. Ill patients, including those receiving sulfonamide therapy, apparently are not good candidates for such a routine. Such patients, in the past, frequently received no specific therapy, and it was the impression that their illnesses were unduly complicated by the additional burden, pain, and discomfort of engorged breasts. Our interest in the use of stilbestrol was stimulated by the enthusiasm of some writers and we were led to try it on a small group of patients. The results obtained in these few warranted further application of this method. As a survey of the literature failed to reveal many carefully controlled studies, we were prompted to conduct the present investigation.

Historical Review

Since Dodds and his co-workers, in 1937 and 1938, presented stilbestrol and related compounds as therapeutic estrogens, there has been an extensive study of the drug and a rapid accumulation of reported material. A total of 1,715 clinical cases on the use of stilbestrol and its effect on lactation have been reported. In addition, well over one hundred additional cases employing testosterone and other drugs, including triphenylethylene, hexestrol and dinoestrol, have appeared in the literature. Considerable data are also available on biologic experimentation in this field.

The original investigations with synthetic preparations having estrogenic actions were made on ovariectomized rats. Of the drugs studied, 4-4' dihydroxy α β diethylstilbestrol (stilbestrol) was found to be an effective potent substance. Studies by Foley and Watson in England,

and by investigators in this country, clearly showed that lactation could be inhibited in rats by the administration of stilbestrol, as well as by estradiol or by testosterone. Further controlled animal experiments revealed changes in the pituitary glands and less distention of the mammary glands, yet with an increase of lactogenic substance in the blood titre. It would seem evident from a review of these and other studies that suppression of lactation probably is not obtained by suppression of the lactogenic hormone in the pituitary. The exact mechanism still remains unsolved.

Early clinical reports were limited in scope, and were of value chiefly in pointing out the various indications and applications of the drug. From the outset, reports were uniformly optimistic concerning the use of stilbestrol for control of lactation and breast symptoms in those cases where breast feeding was not carried out. British authors demonstrated that different results were to be expected when the drug was administered prior to the onset of lactation as compared with its administration after lactation had been established. Early reports were based on small series of cases; more recently extensive studies have appeared. Connally and his co-authors observed, along with uterine and endometrial changes, the suppression of lactation in over 70 per cent of their patients. The authors stated that none of the patients complained of engorged or painful breasts. More recently, Muckle's study of seventy-five cases revealed that on a uniform plan of medication, breast engorgement was relieved in twenty-four to thirty-six hours and that lactation was effectively controlled.

Several other articles recording fifty cases or more have been published. Clahr reported follow-up studies in a series of one hundred and twenty cases. His best results in preventing lactation were in a group of patients in whom the administration of stilbestrol was continued for more than two weeks. Where the drug was given because of engorgement, relief of pain was obtained within twenty-four hours in seventy-six per cent of cases. Stewart and Pratt, using various endocrine preparations, concluded from a detailed study that inhibition of engorgement was not synonymous with inhibition of lactation; the former was achieved in all their cases while the latter was doubtfully obtained. Abarbanel and associates studied controlled series of cases. In both control and stilbestrol treated groups nursing of the baby was continued. But little comparative advantage was noted, even in those cases receiving large daily doses of stilbestrol. Diddle and Kettel reported another controlled series. They found marked engorgement, so-called "failures," in but seven of ninety-two cases when the drug was started early; whereas, in their controls only two of seventy-five patients had no engorgement.

In summary, it is evident that stilbestrol has real therapeutic advantages. But in what particular features it can be expected to improve our care of the post-partum breast is not altogether clear. As might be expected, its use cannot obtain satisfactory results when suckling is continued. Many reports were of a general nature and based on impressions rather than on reliable statistical data. It is unfortunate, too, that differentiation was not always made between engorgement, pain, and lactation in considering the results that were obtained. Overlooked variables in clinical studies often confuse the picture and tend to vitiate

the conclusions. In all, only two investigations were carried out with control series.

Materials and Methods

From November 1, 1942, to June 1, 1943, one hundred and ninety patients were studied in whom breast feeding was undesirable or contraindicated for one or more reasons. (Table I.)

TABLE I. INDICATIONS FOR AVOIDANCE OR DISCONTINUANCE OF LACTATION

INDICATION	NUMBER OF CASES	PERCENTAGE
Personal preference	51	33.4
Dead baby	30	19.6
Premature baby and/or twins	21	13.7
Flat or inverted nipples	12	7.5
Heart disease	10	6.5
Sick baby	6	3.9
Toxemias	5	3.3
Previous breast abscess, tumor, or mastitis	5	3.3
Puerperal infection	4	2.6
Syphilis	2	1.3
Respiratory infection	2	1.3
Pulmonary tuberculosis	2	1.3
Diabetes	1	0.6
Hyperthyroidism	1	0.6
Chicken pox	1	0.6
Total	153	99.5

The patients in whom treatment was initiated before the onset of lactation were divided into three main groups of fifty each. Patients in control group 1, designated C-1, were given no therapy whatsoever other than analgesics to relieve pain as required. Patients in control group 2, C-2, were treated with breast binders, ice bags, sedatives as indicated, restriction of fluids to 1,500 c.c. daily for three to four days and saline catharsis. Patients in the stilbestrol treated group, S-p, were given twenty milligrams of stilbestrol in divided doses according to the following schedule: 10-5-5 milligrams, each dose being separated by a twenty-four-hour period. The drug was started either on the day of delivery or the first day post partum. These patients received no other form of therapy such as binders, ice bags, etc., and there was likewise no limitation of fluids. One group of twenty-one patients, designated S-r, wherein lactation had been established and stimulated by temporary suckling, was treated with stilbestrol on the regime outlined above. Fifteen other patients who had nursed were used as a control group utilizing either no therapy or the binder routine. Four patients with nonsuppurative mastitis were treated with stilbestrol alone.

Our study endeavors to answer the following questions:

1. Is lactation inhibited when stilbestrol is administered to puerperal women prior to the onset of lactation?
2. Is breast engorgement obviated in these patients?
3. Is the pain associated with engorgement eliminated?
4. Is stilbestrol of any benefit in suppressing lactation once it is established?
5. Can stilbestrol be used with benefit in the treatment of nonsuppurative mastitis?

The results obtained in this study are based on a total of 1,888 daily examinations of patients' breasts whose babies were not allowed to nurse. A separate record covering the period of hospitalization was made for each patient. Patients who were observed less than seven days were excluded from the study. Several patients were observed for twenty-four or more days. This is particularly noteworthy in the stilbestrol group. The daily examinations were made by the authors only, and no data were drawn from nurses' notes. All notations concerning pain, engorgement, lactation and erythema were based on jointly accepted criteria. In the beginning of the study the authors checked one another's findings in order to insure uniformity of opinion.

All notations were recorded in comparative figures of from one to four plus. Pain was evaluated both by the patient's subjective complaints, and objectively by the tenderness which was elicited when the patient's breasts were palpated by the observers. Engorgement was measured by the degree of firmness of the breasts. In the event that one breast was more tense than the other, the greater degree of tension was recorded in every case. Erythema was noted according to the degree of redness and the extent of the area involved. Lactation was graded by the amount of leakage of milk in conjunction with the amount that could be expressed from the nipples by the examiner. The temperature recorded daily represented the highest registered mouth temperature for the twenty-four-hour period.

Discussion

In this clinic we advocate breast feeding for newborn infants. However, it is not our practice to insist on breast feeding in patients who, for some reason, are strongly opposed to nursing their offspring. The indications in this study for excluding nursing are listed in Table I. We believe our indications are representative of those commonly encountered in both clinic and private practice. As it is noted, the largest group of patients included in our study was those who did not wish to nurse their babies. The next largest group was represented by those mothers who had dead born or stillborn infants; and the third group comprised those who had been delivered of premature infants and twins. It might be pointed out that no patient was urged not to nurse her baby for the purpose of this study. It is assumed that all the patients observed in our study probably would not have nursed their babies otherwise.

In the particular portion of the study devoted to the effect of stilbestrol on inhibition of lactation and freedom from pain and engorgement, there were one hundred and fifty patients. Of these 43.4 per cent were primiparas and 56.6 per cent were multiparas, the multiparas having previous nursing experience. The comparative distribution is

TABLE II. DISTRIBUTION OF PARITY IN EACH GROUP

	STILBESTROL		CONTROL-1		CONTROL-2	
	NO OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
Primiparas	20	40	27	54	18	36
Multiparas	30	60	23	46	32	64
Total	50	100	50	100	50	100

given in Table II. History of previous nursing record was obtained in the multiparas. It was thus possible to distribute equally, in the control and stilbestrol prescribed groups, those patients in whom adequate lactation could be expected, and thereby minimize this one variable when comparing results of the study.

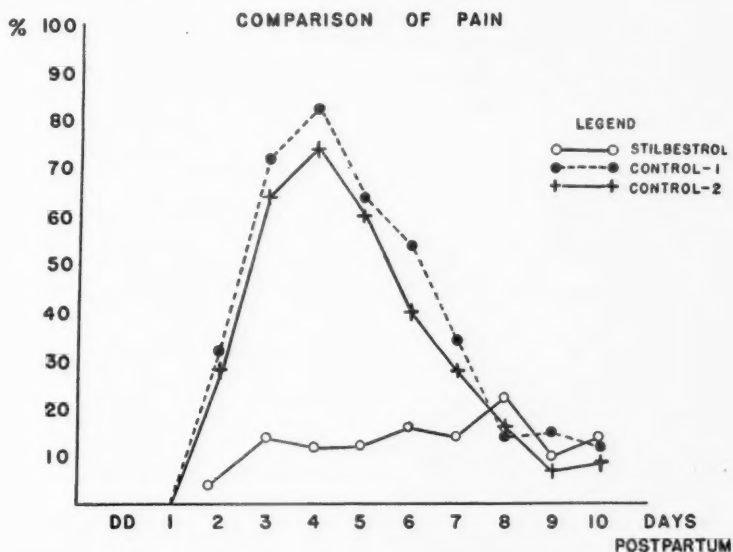


Chart 1.—Comparison of total number of patients with breast pain of all degrees in stilbestrol treated patients (S-p), control group with no therapy (C-1), and control group with conventional treatment (C-2).

Chart 1 demonstrates the percentage incidence of breast pain as it occurred in each of the three groups. The degree of pain varied and clinically was measured as ranging from one plus to four plus in intensity. Pain occurred on the fourth day in 82 per cent of the control group, C-1, that had no treatment; by the tenth day only 10 per cent in this group complained of pain. A similar incidence was recorded in the control group, C-2, receiving conventional treatment; the maximum incidence was only 8 per cent below that of the former. Thus, from a study of this graph, conventional treatment appears to obtain only slightly better results. Contrastingly, the occurrence of pain in the group treated with stilbestrol, S-p, was strikingly low.

Further analysis of each group was made in order to compare the degree and intensity of breast pain. Chart 2 reveals that pain in the

group treated with stilbestrol was, for the most part, of minor intensity, particularly in the latter days. Charts 3 and 4, on the other hand, show that from 30 to 40 per cent of the pain developed, in control groups, was of relatively intense character.

A comparison of the total number of patients with breast engorgement is shown in Chart 5. One notes that from 90 to 94 per cent of the patients in both control series had engorged breasts. This maximum en-

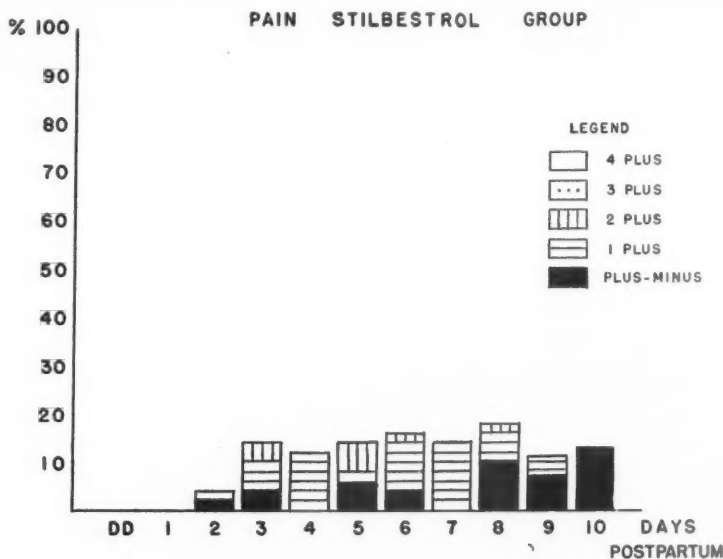


Chart 2.

Charts 2, 3 and 4.—Occurrence of breast pain, graphed according to degree of intensity from plus-minus to four plus, in each of the study groups.

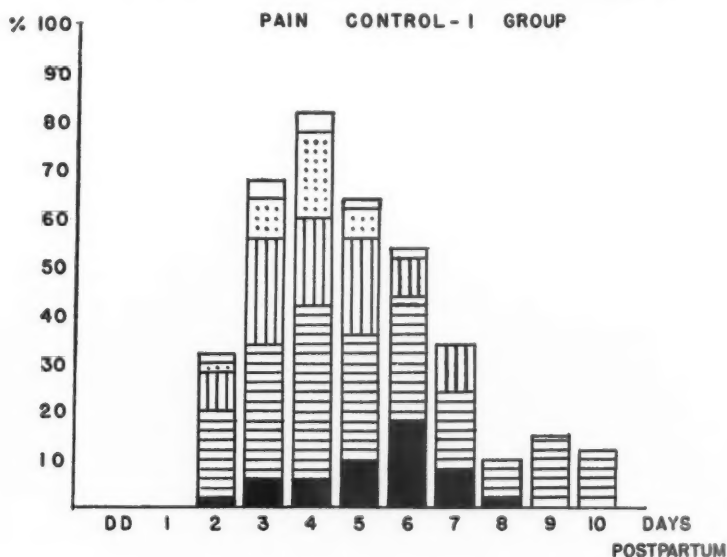


Chart 3.—For legend see above.

gorgement is evident on the fourth and fifth post-partum days, then rapidly declines to one-fourth of this value by the tenth day. Patients on stilbestrol therapy in comparison, were relatively free of engorgement. Breast congestion in this group, while delayed in some instances, at no time occurred in over 37 per cent of the cases. Furthermore, the breast tension was observed to be of shorter duration than in the control series.

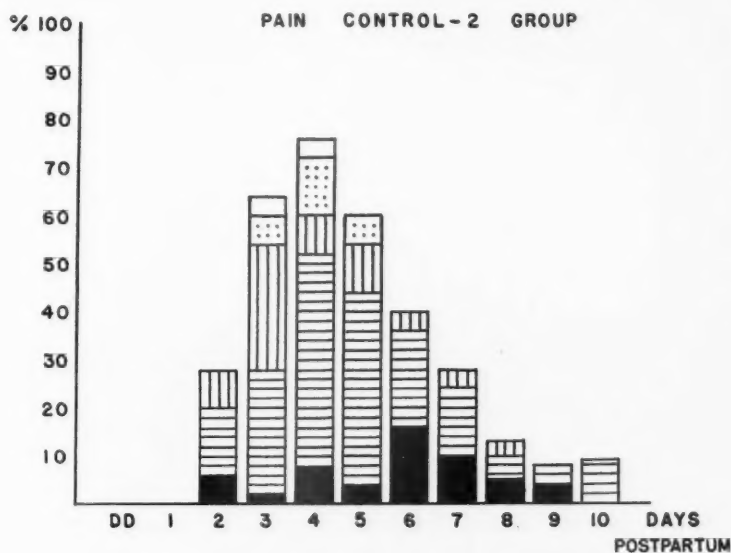


Chart 4.—For legend see opposite page.

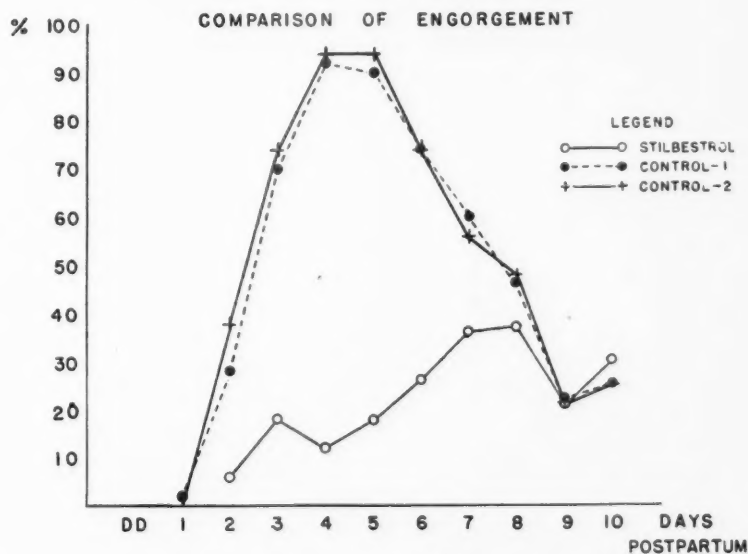


Chart 5.—Comparison of total number of patients with breast engorgement of all degrees in stilbestrol treated patients (S-p), in control group with no therapy (C-1), and in control group with conventional treatment (C-2).

Charts 6, 7 and 8 contrast the relationship of the degree of the intensity of engorgement to its occurrence in the puerperium in each of the three groups. Engorgement in the stilbestrol treated group is shown to be of moderate to mild degree throughout. In the control group receiving no treatment, breast congestion was found to be somewhat more intense. Studying the third series treated by conventional measures, there is noted a close similarity of moderate and severe engorgement to that of the second series.

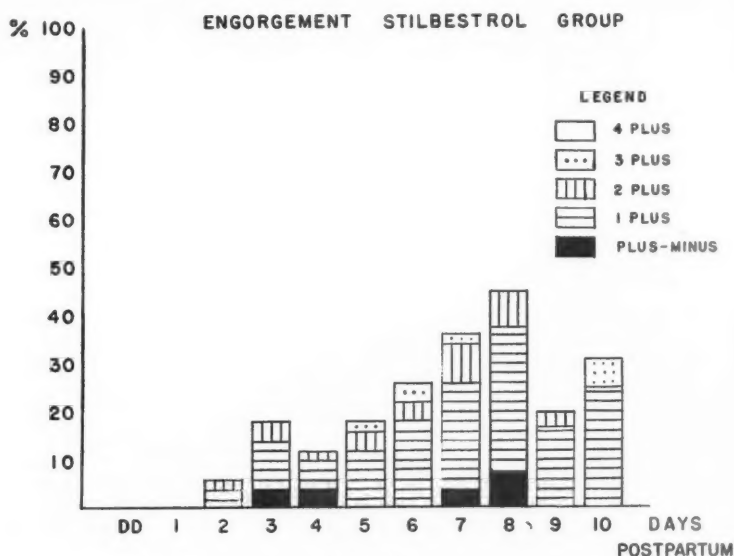


Chart 6.

Charts 6, 7 and 8.—Occurrence of breast engorgement, graphed according to degree of intensity, from plus-minus to four plus, in each of the study groups.

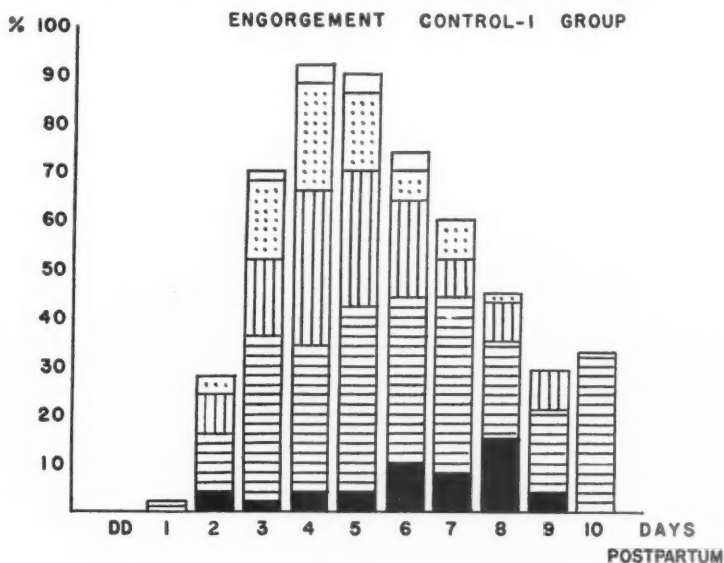


Chart 7.—For legend see above.

Lactation in each of the three classes studied is compared in Chart 9. The stilbestrol treated group exhibited a relatively low curve of lactation reaching a peak of 43 per cent on the eighth day. While in the control group omitting treatment, a high value of 88 per cent of patients was found to be lactating on the fifth day, the incidence then rapidly dropping off. A similar response, though less marked, was exhibited by the last group receiving conventional treatment; more mothers lactated

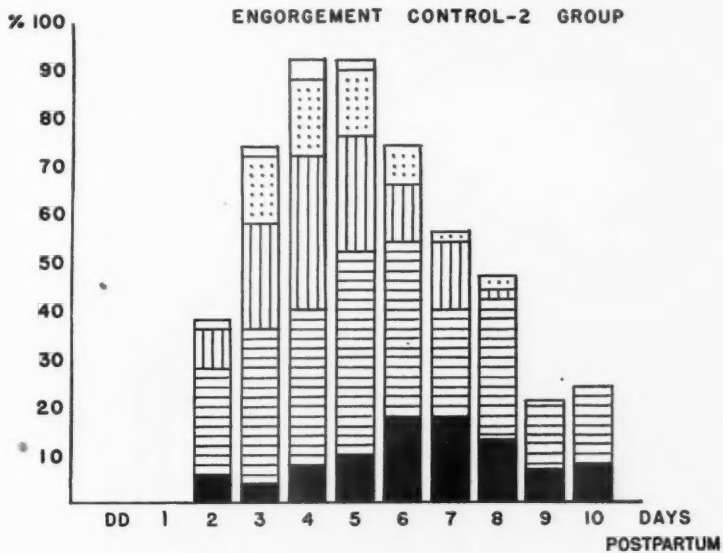


Chart 8.—For legend see opposite page.

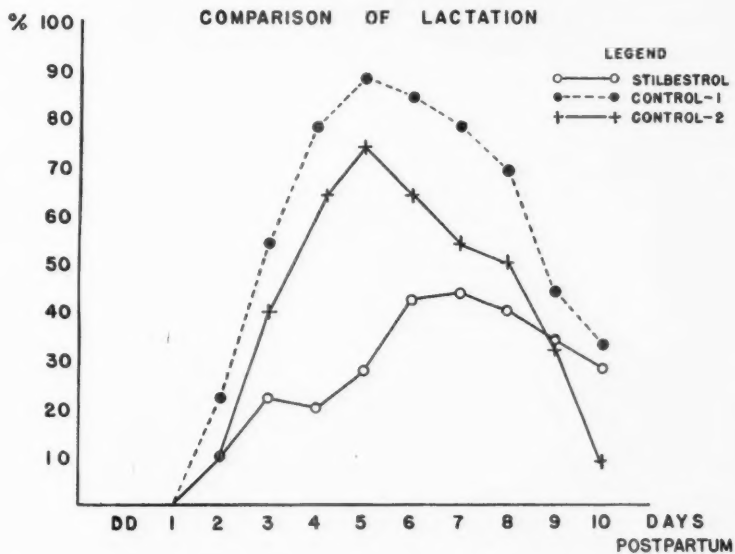


Chart 9.—Comparison of total number of patients with lactation of all degrees in stilbestrol treated patients (S-p), in control group with no therapy (C-1), and in control group with conventional treatment (C-2).

again on the fifth day, followed by a sharp decline. In this chart are recorded curves similar to those of engorgement recorded in Chart 5 with a rise and fall of engorgement approximating rise and fall of lactation. So, for example, in stilbestrol treated cases, a complementary late rise of lactation is seen with a late transient rise in breast engorgement. Further study of these charts reveals the equal efficacy of stilbestrol in partially preventing breast engorgement and lactation.

The degree of lactation in each series was studied and compared in Charts 10, 11 and 12. It may be thus further observed that patients

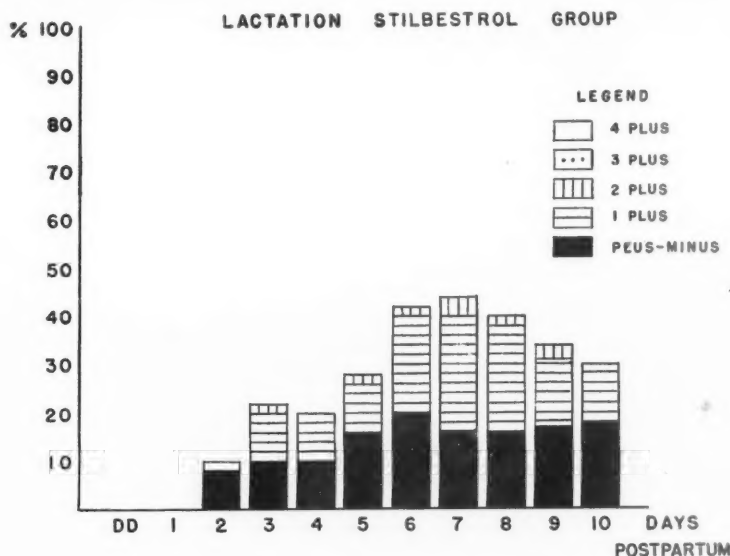


Chart 10.

Charts 10, 11 and 12.—Occurrence of lactation, graphed according to degree, from plus-minus to four plus, in each of the study groups.

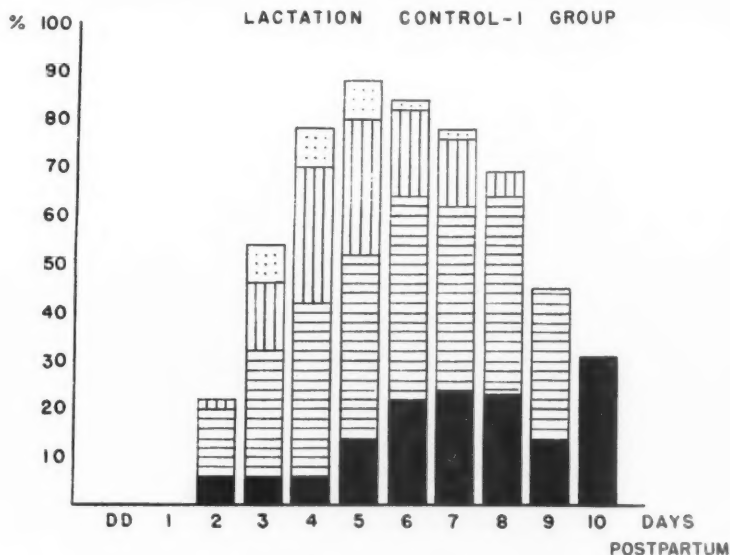


Chart 11.—For legend see above.

in both control series exhibited a greater degree of lactation, particularly those without treatment, than in the stilbestrol treated series. In other words, not only were there fewer cases of lactation in the stilbestrol treated patients, but of those lactating, the degree was noticeably less marked.

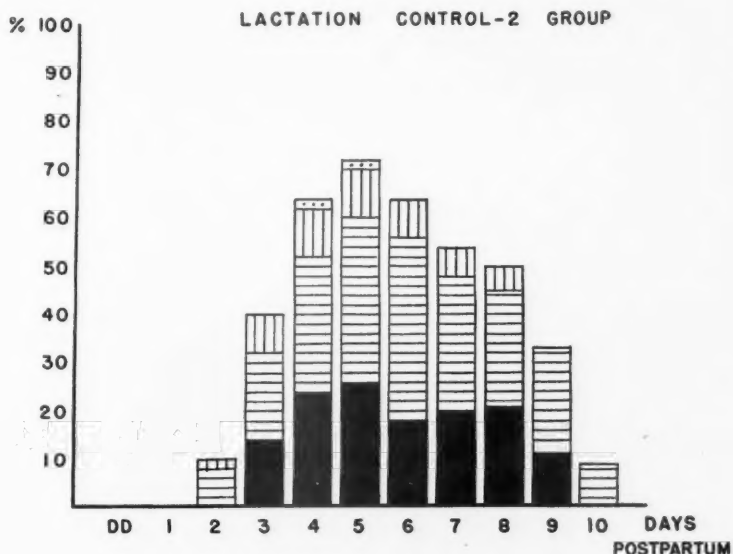


Chart 12.—For legend see opposite page.

The occurrence of erythema in all our patients was minimal. This complication was present in 4 per cent of the stilbestrol treated cases, in 14 per cent of the control cases omitting treatment, and in 8 per cent of the control cases on conventional prophylactic measures. Combining the two control groups, an average figure of 11 per cent was found to be almost three times the incidence in the stilbestrol group. Yet in none of these cases was the erythema severe, nor did it accompany the other classical features indicative of mastitis.

As noted above, the highest daily temperature was recorded on our study sheet. These temperature elevations were in turn correlated with breast engorgement, with one-day fevers, and with morbidity due to all causes. In view of the diversity of opinion regarding the occurrence of fever due to engorgement, we use the term "breast morbidity" where there is an elevation in temperature to 38.0°C ., or more on any two days, associated with breast engorgement, and where there is no other explanation for the fever. "Engorgement with fever" represents a single day fever coincident with breast engorgement. Total morbidity is that puerperal morbidity due to all causes. In Table III is listed the occurrence of each in the three study groups. Single day fevers associated with engorged breasts occurred in equal frequency in each group. Actual "breast morbidity" was negligible. Total morbidity of the one hundred and fifty patients in this study was essentially that of the clinic as a whole, namely, 10 per cent.

Analyzing our figures from the viewpoint of onset of pain, engorgement and lactation, we find, as has been the general impression, that in

TABLE III. OCCURRENCE OF POST-PARTUM FEVER AND MORBIDITY IN 150 CASES

	STILBESTROL		CONTROL-1		CONTROL-2	
	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
Total Cases	50	100	50	100	50	100
Engorgement with fever	4	8	5	10	5	10
Breast morbidity	0	0	1	2	2	4
Total morbidity	8	16	4	8	3	6

Average total morbidity 150 cases = 10%



Chart 13.

Charts 13, 14 and 15.—Comparison is made of the number of days required for the subsidence of pain, engorgement, and lactation; the stilbestrol treated groups (S) in contrast to the control groups (C).

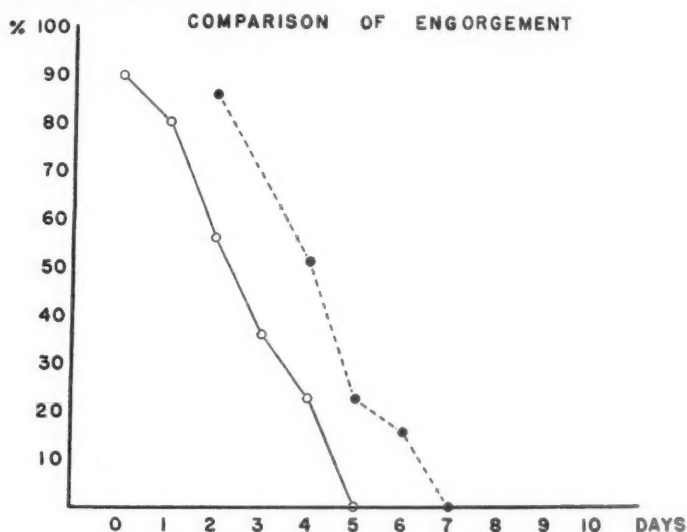


Chart 14.—For legend see above.

all the control cases the average day of onset was the third post-partum day. It may be pointed out again that our stilbestrol treated patients demonstrated an average delay of three days; that is, breast symptoms and related findings developed on the sixth day.

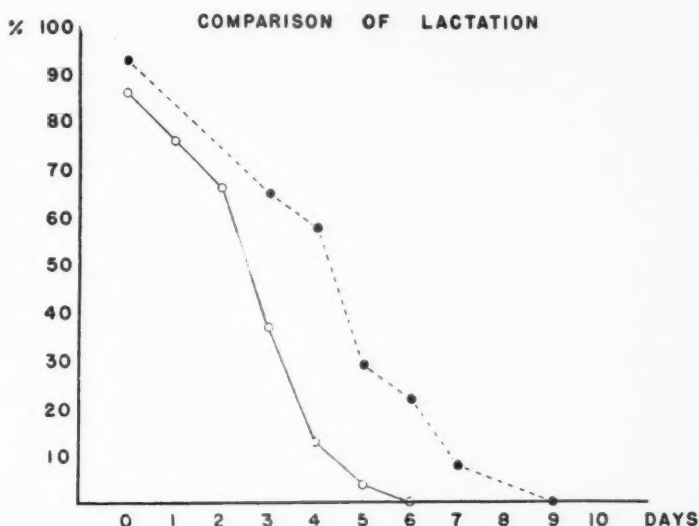


Chart 15.—For legend see opposite page.

TABLE IV. FREEDOM FROM PAIN, ENGORGEMENT, AND LACTATION IN 150 CASES

	STILBESTROL		CONTROL-1		CONTROL-2	
	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
Total Cases	50	100	50	100	50	100
Patients with no pain	23	46	2	4	0	0
Patients with no engorgement	20	40	3	6	0	0
Patients with no lactation	13	26	1	2	7	14

Table IV reveals, in a striking manner, the efficacy of stilbestrol therapy. In the control-1 group, over the entire post-partum hospital course, only 4 per cent of patients was free of pain, and only 6 per cent was free of engorgement; there were none in the control-2 group; while in the stilbestrol group approximately two out of every five individuals were entirely free of pain and free of engorgement. As might be expected, the freedom from lactation in this latter group, though less marked, was significantly better when compared with controls.

A smaller series of cases was studied, again with accompanying control series, to determine the suppressing effect of stilbestrol in cases where lactation had been established. In Chart 13 is recorded the number of days to relief of pain. Patients receiving stilbestrol were entirely relieved of pain within four days. A similar decrease of pain is noted in control groups, save that in a few instances pain persisted until the seventh day. Engorgement was studied and, noted in Chart 14, was

found to subside more rapidly by approximately two days in the stilbestrol treated cases than in the control cases. Chart 15 portrays a similar and rapid decline in lactation. By the sixth day, in the stilbestrol treated patients all lactation had ceased; by the ninth day this was likewise true of the comparative control group. Where nursing and/or lactation had been established, we can thus point out that administration of stilbestrol has a definite though limited value in hastening the subsidence of annoying features of pain, engorgement, and lactation.

In this study only three cases of breast fever were recorded, one in the stilbestrol treated group and two in the controls, too few for proper differential evaluation. So also only six cases of erythema were found, three each in the stilbestrol treated and in the control series.

During the course of this seven-month study period, we unfortunately were able to treat with stilbestrol only a few cases of mastitis over a period adequate for analysis. It is our impression from this limited experience with stilbestrol, comparing results with those attained using conventional measures, that the former probably has little beneficial effect in the treatment of mastitis. While we are, as yet, in no position to express a final opinion, we would not recommend the drug, save as an adjuvant, in the treatment of mastitis.

A final commentary may be mentioned. In no case of administration of stilbestrol did we observe nausea or vomiting, or other evidence of sensitivity to the drug. This observation is in agreement with similar reports in the literature. Like others, we have no real explanation for this peculiar immunity.

Summary

One hundred and ninety patients, including comparative control groups, who did not nurse or in whom nursing was discontinued, were studied to determine the therapeutic effect of stilbestrol on breast pain, engorgement, lactation and erythema. Patients were evenly distributed on the basis of previous nursing record. Separate studies were carried out on patients where lactation had been established and on those selected prior to the onset of lactation. In all, 1,888 separate-daily examinations were carried out by the authors.

Conclusions

1. Stilbestrol, by comparison, was found highly effective in preventing the development and minimizing the intensity of breast pain.
2. Engorgement was reduced in incidence, in the stilbestrol group, to one-third that of the controls; it was less intense, and developed later in the puerperium.
3. Lactation, while frequently delayed in onset, was definitely, though less markedly, depressed than were the other features studied.
4. Erythema was found in but one-third the number of stilbestrol treated cases, compared with controls.

5. Fevers associated with breast engorgement occurred in approximately the same number of cases in each study group.

6. Entire freedom from breast pain and engorgement in the stilbestrol treated series was striking in contrast with the control series.

7. Conventional therapeutic measures were found, comparing results in the two control groups, to be of little benefit save in the partial reduction of lactation.

8. Separate control studies on the therapeutic effect of stilbestrol once lactation had been established showed that the treatment held but slight advantage in the relief of breast pain; that relief from engorgement and subsidence of lactation was definitely, though not markedly, bettered.

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THE ABSORPTION OF STEROID HORMONES FROM THE ORAL MUCOUS MEMBRANES, WITH SPECIAL REFERENCE TO THE SUBLINGUAL ADMINISTRATION OF PROGESTERONE

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IN THE search for more convenient modes of administration of the steroid hormones, attention has been directed in recent years to the absorptive capacity of the oral mucous membranes. Freudenberger and Howard¹ were the first to call attention to this route for steroid hormones when they found that pregnancy urine dropped in the mouths of immature rats, caused premature opening of the vagina. Since the amount retained in the mouth was scarcely more than the amount necessary to moisten its lining, they concluded that the active principle in pregnancy urine was absorbed through the oral mucous membranes. Looking back upon this experiment, it seems possible that what was absorbed was chorionic gonadotropic hormone, rather than estrogen; but in any case the observation was sufficient to call attention to the possibility of absorption of the steroid hormones directly from the oral cavity.

Estrogens

Gysi² and Engels,³ as cited by Miescher and Gasche,⁴ and Salmon and Geist⁵ were the first to apply this method clinically. Salmon and Geist, using a solution of α -estradiol in propylene glycol, were able to produce vaginal cornification in 8 estrogen-deficient women with daily doses of 0.2 to 0.3 mg. for 7 days. Herrnberger⁶ and Reifferschied and Schmidt⁷ used alcoholic solutions of estradiol to obtain endometrial proliferation in menopausal and amenorrhoeic women with doses ranging from 6 to 15 mg. per day for 6 to 20 days. Giesen⁸ obtained similar results with tablets allowed to dissolve under the tongue. Albers⁹ reported that when estradiol was administered sublingually, twice the intramuscular dose was required to produce equal lowering of the serum calcium. Joël¹⁰ was able to produce endometrial proliferation in women who had received previous x-ray therapy with 4 to 6 mg. daily for 15 days in the form of sublingual tablets. Hall¹¹ reported vaginal cornification in menopausal women with doses of estradiol benzoate in propylene glycol of 0.2 mg. daily for 10 to 14 days (totaling 2.0 to 2.8 mg.) as compared with a total of 1.666 mg. given by injection in two doses 5 to 7 days apart. Forty-one per cent of his patients showed relief of symptoms or improvement with this dose and route of administration, to the same degree as after administration by injection, while 58 per cent showed slight recurrence of symptoms. He concluded that with equal doses the results would have been equal, but that individualization of doses is necessary. Diddle, Nagyfy, and Sells¹² found that with frequent sublingual administration α -estradiol is as effective in the suppression of lactation as by injection.

Hohlweg (cited by Giesen⁸) found that a sublingual dose of estradiol 35 to 45 times the subcutaneous dose and 1/10 of the oral dose produced

estrus in castrated rats. Reifferschied and Schmidt⁷ reported the sublingual dose in rats to be $\frac{1}{6}$ the oral dose of estradiol glucoside and $\frac{1}{3}$ that of estradiol. Miescher and Gasche⁴ found that the effective dose of an alcoholic solution placed under the tongue was 1/10 to 1/20 of that by stomach tube when measured by the increase in weight of the uterus in castrated rats. This dose they state is nearly equal to the dose by injection or by inunction. Further they maintain that division of doses has little or no effect.

Castrodale, Loeffel, and MacBryde¹³ reported that diethylstilbestrol in propylene glycol solution relieved menopausal symptoms in 11 out of 17 patients in the same dose as that effective orally, or by the gastrointestinal route; that is to say, about twice the intramuscular dose. One patient indeed had greater relief with the sublingual than with other forms of medication.

It would seem that, with the exception of Hohlweg's report cited by Giesen,⁸ whenever a comparison of the minimal effective dose has been made estrogens and stilbestrol are found to be about equally effective by sublingual administration as by injection. It should be also noted that the dose may vary from one individual to another.

Desoxycorticosterone

Anderson, Haymaker, and Henderson,¹⁴ Anderson and Haymaker,¹⁵ and Turnoff and Rowntree¹⁶ maintained patients with Addison's disease on desoxycorticosterone acetate in propylene glycol solution containing 20 per cent alcohol, with doses usually less than twice the intramuscular dose. Thorn, Greif, Coutinho, and Eisenberg,¹⁷ using the hormone in pure propylene glycol, found that their patients required at least 3 times as much sublingually as intramuscularly. In 1942 Thorn, Dorrance, and Day¹⁸ reported that the dose of sublingual tablets and solutions was 6 to 8 mg. daily as compared to 2 mg. intramuscularly and to a calculated dosage of 1.2 mg. daily for implanted pellets. Clinton and Thorn¹⁹ reported only slight rises in plasma volume in normal subjects given sublingual tablets, whereas significant increases were obtained by injection of comparable amounts of the hormone. Wilson,²⁰ using $1\frac{1}{2}$ to 7 times the intramuscular dose in 4 patients, reported return of what he felt were insufficiency symptoms in 3 patients. The fourth patient, the only one on the lowest dose, died of an intercurrent infection during treatment. Under these conditions the requirement for desoxycorticosterone is known to increase. In the others the symptoms may have been due to the large overdoses used, for as Engel, Cohn, and Soffer²¹ mention, overdosage of desoxycorticosterone is often associated with symptoms difficult to distinguish from incipient adrenal insufficiency. These authors tried the sublingual method on 5 patients and were able to maintain 2 patients with extremely mild adrenal insufficiency on doses no larger than the intramuscular dose. Two patients could not be maintained at this level. One patient developed incipient insufficiency symptoms on twice the injection dose. The sublingual doses, however, were apparently not divided into 4 or 5 per day as recommended by the other authors. According to Schachter,²² Thaddea²³ and Heni²⁴ in Germany have reported agreement with the results of Anderson and Haymaker. Thorn et al.¹⁷ reported a 3 to 1 ratio of sublingual to intramuscular dosage in adrenalectomized dogs. Cleghorn, Clarke and Greenwood²⁵

were unable to maintain adrenalectomized dogs on doses as high as 4 times the standard intramuscular dose, but they admitted that adequate precautions to prevent swallowing of the medication were not used.

It would seem then that with the exception of Wilson's somewhat questionable results, it is possible to maintain mild cases of adrenal insufficiency on doses from the same to twice the intramuscular dose. For more severe cases doses from 3 to 4 times the intramuscular dose are needed. Again there seems to be individual variation in the dose needed.

It has been pointed out (Henderson, personal communication) that the quantitatively different results obtained by some of the workers, namely Anderson, Haymaker, and Henderson on one hand, and Thorn and co-workers on the other, may have depended on a difference in the absorption of the hormone solution. Thorn et al. dissolved the desoxycorticosterone in pure propylene glycol, having a surface tension of 42 dynes per square centimeter, whereas Anderson, Haymaker, and Henderson used propylene glycol diluted with 20 per cent absolute alcohol, a mixture which has a surface tension of only 31 dynes per square centimeter and which therefore would be more readily absorbed.

Androgens

Joël²⁶ used sublingual methyl testosterone tablets for the relief of menopausal symptoms in women in doses ranging from 5 to 30 mg. daily. Spence²⁷ reported maintenance of potency in a male castrate with sublingual methyl testosterone tablets on a dose 4 times the injection dose. Lisser, Escamilla, and Curtis²⁸ compared the efficacy of sublingual methyl testosterone, testosterone propionate, and testosterone in propylene glycol. In 4 sexually retarded cryptorchid males, they were able to establish sexual maturity with $\frac{1}{3}$ the oral dose or about $1\frac{1}{2}$ times the intramuscular dose. In 5 eunuchoids the effective sublingual dose was equal to 3 times the injection dose. Testosterone was more effective at a given small dose than were its esters. Miescher and Gasche,²⁹ however, found that in castrate rats methyl testosterone was 3 times more effective than testosterone when administered sublingually. They also reported that as with the estrogens division of doses was not important.

From these experiments it appears that average effective dose of the androgens administered sublingually is about 3 times the intramuscular dose. Hurxthal³⁰ reported more recently that for maintenance purposes in eunuchoid patients, sublingual administration of testosterone in propylene glycol compares favorably with intramuscular injection of the same compound in oil, in some cases but not in others. About 3 times as much is needed as by pellet implantation. Again it will be seen that there is more individual variation with the sublingual route of therapy.

Pregneninolone

Joël¹⁰ was able to produce bleeding in patients previously treated with sublingual estrogens with sublingual tablets of pregneninolone in doses $3\frac{1}{2}$ times the intramuscular dose of progesterone.

In general, all these experiments suggest that with the exception of the estrogens, which appear to be equally potent sublingually, the average sublingual dose of the steroid hormones is 3 to 4 times the intramuscular dose. In all, there seems to be considerable individual variation as to the effective dose. Furthermore, it seems best to split the dosage into 4 to 5 small doses a day.

Progesterone: Experiments and Results

In order to test the efficacy of the sublingual administration of progesterone, the present author carried out hormone assays on rabbits and on Rhesus monkeys. Solutions of crystalline progesterone in propylene glycol containing 20 per cent absolute alcohol (such that the concentration of the hormone was 10 to 20 mg. per c.c.) were used as the test substance.

TABLE I. PRODUCTION OF PROGESTATIONAL ENDOMETRIUM IN THE RABBIT BY ADMINISTRATION OF PROGESTERONE IN PROPYLENE GLYCOL

MODE OF ADMINISTRATION	TOTAL DOSE	ENDOMETRIAL RESPONSE
Subcutaneous	0.5 mg.	+++
		+++
		+++
		++++
		++++
Subcutaneous	1.0 mg.	++
		+++
		++++
		++++
		++++
Sublingual	1.0 mg.	0
		0
		0
		0
		+
Sublingual	2.0 mg.	++
		++
		+++
		++++
		++++
Sublingual	3.0 mg.	+
		+
		++
		++
		++++
Sublingual	4.0 mg.	++
		++
		++
		++
		+++
Sublingual	8.0 mg.	+
		++
		++
		+++

Rabbits.—In this series of experiments the efficacy of sublingual and subcutaneous administration of progesterone in propylene glycol was compared. Thirty-five assays for progesterone were done on mature

virgin female rabbits according to the standard method described by Corner and Allen.³¹ The progesterone-propylene glycol solution was diluted to concentrations of from 0.5 mg. to 8 mg. per c.c. with propylene glycol containing 20 per cent absolute alcohol, and administered 3 times daily for 5 days. For sublingual use, the solution was administered in doses of 1/16 c.c. from a tuberculin syringe fitted with a blunt 18 gauge needle by inserting the tip of the needle under the tongue and injecting the full dose at one time. The amount of solution given subcutaneously was also 1/16 c.c.

As may be seen from Table I, the amount of endometrial response to progesterone given sublingually was extremely variable, except with the smallest dose (total 1 mg. in 5 days), which was almost uniformly ineffective; in only one instance was even the slightest response elicited. When administered subcutaneously, however, a full response could be produced fairly regularly with 0.5 mg. A nearly full response could be obtained from time to time on all sublingual doses from 2 to 8 mg. In this small series, however, the best response was obtained with the 2 mg. dose.

It must be admitted that the technique of administration employed with the rabbits did not involve as great protection against swallowing of the dose or loss of a portion of the dose from the mouth as the technique employed with the monkeys (see *infra*). The presence of slight variation in the response even with the subcutaneous route, however, tends to support the belief that progesterone in this type of solution (designed for rapid absorption) produces variable results; for when administered subcutaneously in oil (a medium designed for slow continuous absorption), the response is more constant (Corner³²).

The full response obtained with subcutaneous administration of a total of 0.5 mg., given 3 times daily, agrees favorably with the statement of Pineus (cited by Corner³²) that by giving progesterone in oil twice daily the minimal effective dose can be reduced to 0.67 mg. When administered subcutaneously, therefore, progesterone is apparently at least as effective in propylene glycol solution as in oil solution. On the other hand, about 4 times the subcutaneous dose is required if the drug is given sublingually, and the response becomes extremely variable.

Monkeys.—The animals employed were 5 adult female Rhesus monkeys which had gone through one or more menstrual cycles before being castrated. The technique of assay was that used by Corner³³ in determining the minimal effective dose of progesterone administered subcutaneously. In his determination the animals were primed for 10 days with 125 International Units of estrogen subcutaneously daily. When sufficient progesterone was then given, bleeding did not occur until 3 to 8 days after withdrawal of the hormone. The minimal dose required to protect all animals from estrogen-deprivation bleeding was found to be 0.5 mg. daily.

In the present experiments, after 10 to 12 days' priming with estrogen,* progesterone was administered sublingually daily for 10 days by the following technique. The mouth was pried open with the tongue retracted, and the solution dropped into the sublingual space on opposite sides of the frenum. The animal was not released until after the solution disappeared or the floor of the mouth filled with saliva (usually about 15 seconds). No active swallowing movements were noted imme-

*Used in the form of Amniotin (Squibb).

diately. Since the solution employed has a surface tension of only 32 dynes per sq. cm., absorption probably took place before any of the material could be swallowed. The dose, varying from 0.05 to 0.1 c.c. (0.5 to 2 mg. of progesterone), was administered from a tuberculin syringe fitted with a blunt 18 gauge needle which delivered 4 drops per 0.05 c.c. It was found impracticable for technical reasons to give the solution more than twice daily.

In all, 12 trials with the 5 animals were made. As will be seen from Table II, bleeding was inhibited in two animals (182, 147) with 1 mg. daily. Number 182 could be prevented from bleeding when the dose was given once daily. Since No. 147 bled earlier than usual after the withdrawal when 2 daily doses were given, it is felt that the divided dose of 1 mg. represents the minimum effective dose for this animal and that bleeding would not have been inhibited with a single daily dose. When No. 147 was given 2 mg. in 2 daily doses, bleeding following withdrawal of progesterone occurred within the usual limits. In No. 183, 2 mg. given once daily was followed by bleeding on the fifth day of treatment, while 2 mg. in divided doses prevented bleeding until the eighth or ninth day in each of 3 trials. This result was interpreted as indicating that the 2 mg. dose thus divided was very near to the minimal effective dose for this animal. Further division of the 2 mg. dose might have inhibited bleeding in this animal.

TABLE II. INHIBITION OF ESTROGEN-DEPRIVATION BLEEDING BY SUBLINGUAL ADMINISTRATION OF PROGESTERONE TO THE RHESUS MONKEY

ANIMAL	TOTAL DAILY DOSE	SIZE OF EACH DOSE	BLEEDING DURING ADMINISTRATION OF PROGESTERONE	BLEEDING AFTER DISCONTINUING PROGESTERONE
182	1 mg.	1.0 mg. (0.1 c.c.)	Inhibited	Fourth day
678	1 mg.	1.0 mg. (0.1 c.c.)	Sixth day	
182	1 mg.	0.5 mg. (0.05 c.c.)	Inhibited	Fourth day
147	1 mg.	0.5 mg. (0.05 c.c.)	Inhibited	Second day
184	1 mg.	0.5 mg. (0.05 c.c.)	Fifth day	
183	2 mg.	1.0 mg. (0.10 c.c.)	Fifth day	
147	2 mg.	1.0 mg. (0.05 c.c.)	Inhibited	Eighth day
147	2 mg.	1.0 mg. (0.05 c.c.)	Inhibited	Third day
183	2 mg.	1.0 mg. (0.05 c.c.)	Ninth day	
183	2 mg.	1.0 mg. (0.05 c.c.)	Eighth day	
183	2 mg.	1.0 mg. (0.05 c.c.)	Eighth day	
184	4 mg.	2.0 mg. (0.10 c.c.)	Fourth day	

These experiments, as far as they go, suggest that in the Rhesus monkey the ratio between the minimal effective dose sublingually to intramuscularly is of the order of 4 or 5 to 1. Certainly 1 mg. and 2 mg. sublingually do not produce as uniform results in the prevention of estrin-deprivation bleeding as do $\frac{1}{2}$ mg. and 1 mg. administered subcutaneously in oil, as in the experiments of Corner.³³ Experiments on one animal tend to support the belief that giving the total daily dose in several small doses decreases the required minimum effective dose.

Discussion

During the past three years the search for more convenient modes of administering steroid hormones has led to numerous investigations of the possibilities of sublingual administration. From these chiefly clinical reports certain facts concerning this route have become evident. (1) In

order to obtain maximum efficiency, the daily dose should be given in at least 5 or 6 small doses. (2) The size of the effective dose is more variable than by other methods of administration. (3) The size of the effective dose varies with the hormone administered. Estrogens are nearly, if not equally, as effective sublingually as intramuscularly. With the other steroid hormones the sublingual dose is at least 4 times the intramuscular dose. In the case of testosterone, the pure hormone is somewhat more effective than any of its esters. (4) There is no evidence that the tablet form is any more efficient than the solution form except in the matter of convenience to the patient.

The testing of the sublingual method of administration on animals presents many difficulties. One cannot expect them to inhibit swallowing movements, much less hold the mouth open with the sublingual space exposed while the solution is dropped into the mouth. With the Rhesus monkeys it proved impracticable to catch them for administration more than twice daily. Finally, one has to take into consideration a possibly lower capacity for absorption on the part of the oral mucous membrane in the smaller mammals, such as the rabbit.

In spite of the difficulties involved, these experiments are offered as a suggestion that with sublingual administration of progesterone amounts in the order of 4 times the intramuscular dose are required. This result is in the same range as the results reported for other steroid hormones, with the exception of the estrogens.

In rabbits and Rhesus monkeys, however, sublingual administration of progesterone, because of the extremely variable response encountered and the larger doses required, seems to be unsatisfactory. Results reported in the literature for other steroid hormones administered sublingually in humans show more uniform response. It is possible, therefore, that sublingual administration of progesterone in human subjects may prove more reliable than it is in animals.

Summary

1. A review of the literature on sublingual administration of the steroid hormones in various solvents and in tablets is presented. The conclusion is offered that estrogens are equally effective sublingually as by intramuscular administration, while desoxycorticosterone, androgens, and pregnenolone require about 4 times larger doses.

2. Experiments on Rhesus monkeys with progesterone in propylene glycol-alcohol solution administered sublingually produced variable results, but suggest that 4 or 5 times the intramuscular dose is the effective minimum required.

3. Experiments on rabbits with progesterone in propylene glycol-alcohol solution produced extremely variable results which, however, suggest that the ratio of sublingual administration to subcutaneous is, as with the Rhesus monkey, at least 4 to 1.

4. Because of the variability of response and the larger dose requirement, sublingual administration of progesterone to monkeys and rabbits is evidently an unreliable method of administration.

I wish to thank Dr. Edward Henderson of the Schering Corporation, Bloomfield, New Jersey, for providing the progesterone in propylene glycol solution used in these experiments, and Dr. George W. Corner, Sr., for invaluable assistance and advice in carrying out this research.

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EXPERIENCE WITH THE SUPRAVESICAL EXTRAPERITONEAL CESAREAN SECTION (WATERS OPERATION)*

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THE extraperitoneal cesarean operation has a very definite place in obstetric practice, particularly in cases where vaginal delivery has been attempted unsuccessfully or where there is evidence of intra-uterine infection. Sufficient experience with transperitoneal section plus sulfanilamide left in the peritoneal cavity is not yet at hand to indicate whether this latter procedure will or will not eventually replace the extraperitoneal procedure.

Our group of cases represents an attempt by a fairly large group of obstetricians and gynecologists to acquaint themselves thoroughly with the technique of the supravescical extraperitoneal section as described by Waters. Some of our cases would undoubtedly have been sectioned earlier, if we did not have this procedure at our disposal; on the other hand, there were a good many cases that were given a longer test of labor than usual, and thereby delivered vaginally.

In 1939 at a meeting of this society, E. G. Waters¹ reported a series of extraperitoneal operations using a technique whereby the lower uterine segment behind the bladder was approached by sharp dissection of the bladder fascia rather than by blunt dissection and in which he accomplished complete separation of the peritoneal fold from its attachment to the bladder—following the principle of Physick completely. It was this report that initiated our interest and is responsible for our present report. In 1940 J. V. Ricci² described a somewhat similar technique using a coiled-up catheter in the bladder to demarcate that organ instead of distending it with fluid.

The principle of the operation consists in separating the bladder from the attached peritoneal fold and thereby approaching the retro-vesical lower uterine segment. This is made possible by the fact that each of the pelvic organs is covered by several layers of endopelvic fascia; by working between these layers the organs may be separated without injury. The fascial layers over the bladder seem to be multiple but are not distinct separate layers. The transversalis fascia continues down from above and over the bladder and behind the symphysis. Over the bladder it is intimately connected with the prevesical

*Read at a meeting of the Brooklyn Gynecological Society, November 5, 1943.

fascia. The peritoneum reflected over the bladder is firmly adherent to the bladder while the vesico-uterine fold is loosely adherent to the uterus (and thus is easily reflected off the uterus, as in hysterectomy and low flap cesarean section). The point of reflection rises with advancement of labor.

Authors' Modified Technique

The bladder is filled with 150 to 200 c.c. of methylene blue solution; the catheter remains in situ and connected with the container, so that the bladder may be emptied or refilled as desired.

The incision is about four inches long, starting about two inches below the umbilicus and extending to the symphysis; the incision is midline (or left paramedian) and through skin and superficial fascia. The skin is reflected to the left slightly, so that the fascia (anterior rectus sheath) is incised slightly to the left of the midline (in order to avoid injury to the peritoneum when extending the incision upward, and injury to the bladder when extending the incision downward); this incision in the anterior rectus sheath is extended downward to the symphysis, and upward over the rectus muscle to the upper end of the incision. If necessary the pyramidalis muscle is cut. The midline is approached, and the two recti muscles separated, exposing the distended bladder covered with transversalis fascia, and the peritoneal pouch coming down over the bladder dome. The transversalis fascia and the prevesical fascia are incised longitudinally (for about 1½ inches) below the peritoneal reflection; bluntly (with back of knife) these layers are separated laterally and superiorly from the bladder wall and these fascial layers are cut with scissors horizontally (making a T incision). Approaching the left vesico-uterine space inside the bladder fascial covering, the bladder is emptied of most of its contents and the fascia lateral to the bladder is incised longitudinally until the lower uterine segment is reached. A finger is then insinuated behind this fascia medially so as to separate the bladder and its posterior fascial covering from the uterus. The peritoneal fold is now put under tension so that its line of demarcation from the bladder stands out and this line is now incised sharply and carefully thus separating the peritoneum from the bladder. If the peritoneal cavity is accidentally opened, the opening is tied with a plain ligature rather than a suture. This dissection is carried across the top of the bladder from left to right. The bladder is now completely emptied and the fascia over the uterus below the vesico-uterine reflection of peritoneum (which now stands out clearly) is incised horizontally and the peritoneal fold pushed up over the uterus to a point high enough to give ample room for the extraction of the fetus. The uterus is incised in a horizontally crescentic incision (convex downward) and the fetus extracted using the hand as a vectis aided by pressure from above; this is done slowly to avoid extension of the uterine incision. Ergotrate is given intravenously at this point. The placenta is removed and the uterine wound sutured with two layers (second layer, Lembert) of continuous chromic suture avoiding the peritoneal fold superiorly. The bladder is again filled with fluid to make certain that there are no perforations or weak points. Bleeding on the bladder wall is controlled. The peritoneal fold is examined for injury. A Penrose drain is left behind the bladder; the fascia and skin are closed as usual.

Report of Cases

From April, 1939, through early October, 1943, 100 cases of Waters' extraperitoneal section were done. We have divided these into 2 groups, indicated extraperitoneal sections and nonindicated extraperitoneal sections.

Arbitrarily we have chosen the following criteria for the indicated group: the presence of a temperature over 100° F. by mouth, membranes ruptured over 15 hours, or pains for over 24 hours. Our nonindicated cases would ordinarily have had a low flap section. There were 76 cases in the indicated group and 24 in the nonindicated.

In the first group 11 patients had temperatures ranging from 100 to 105° F., 53 cases had ruptured membranes for an average of 43.9 hours; and 61 cases had pains for an average of 48.7 hours. One case in this group of 76 had had an attempted forceps that failed.

There were 93 primiparas and 7 multiparas.

Indications for section for the entire series of 100 cases were: disproportion 44, primary uterine inertia 20, toxemia 8, elderly primipara 7, previous stillbirths 4, cervical dystocia 4, fetal distress 6, dystocia dystrophy syndrome 3, sterility 2, previous section 2. Most of these cases had several factors responsible for doing the section, but the most pertinent one was used for classification.

Anesthesia.—Spinal was used in 67 cases, gas-oxygen-ether in 27 and cyclopropane in 6.

There were 25 different operators in this group. The average operating time was 73 minutes with a range from 35 minutes to 135 minutes. As more experience was obtained, the operating time for each of the operators was considerably reduced.

The average blood loss was estimated to be 350 to 400 c.c. Two cases had an estimated loss of 700 to 800 c.c. and 2 others 1,000 c.c. each. Four patients were given transfusions.

Peritoneal and Bladder Injuries.—Of the 100 cases reported, 36 had one or more openings in the peritoneum. These were usually tied off with a ligature before the uterus was incised. Six of the 36 cases were found to have openings in the peritoneum at the completion of the operation. These 6 cases occurred in the earlier days of our experience and we learned that they were usually due to ligatures on the peritoneum placed under tension or insecurely tied. Openings in the peritoneum, as Waters has indicated, are best treated by ligature rather than suture ligature to avoid microscopic leak in the peritoneal fold through which bacterial invasion might theoretically take place.

Seventeen bladders were injured; fifteen had perforations that ranged in size from very small to quite large; one bladder was markedly thinned out in one area so that the mucosa was exposed; and one case where no injury was observed at the table developed a vesico-abdominal and vesico-vaginal fistula. This last case had profuse bleeding from large veins on the posterior bladder wall close to the lower segment and deeply placed suture ligatures undoubtedly produced sloughing of the bladder wall. All patients made uneventful recoveries. All bladder openings and areas of markedly thinned out bladder wall should be carefully repaired in layers and a retention catheter left in for at least 10 days. Three of our cases had vesico-abdominal fistulas. Two of these are mentioned above and a third one occurred in a case which

had a bladder perforation and was treated improperly: the catheter being removed on the fourth day. It was subsequently replaced for 10 to 12 days and healing occurred. All the fistulas eventually healed with the use of an indwelling catheter.



Fig. 1.—Schematic representation of anatomy, showing horizontal section below peritoneal reflection. 1. Skin and superficial fascia. 2. Anterior rectus sheath. 3. Recti muscles. 4. Fascia transversalis. 5. Bladder wall. 6. Posterior vesical fascia. 7. Anterior uterine wall. 8. Peritoneum. 9. Symphysis.

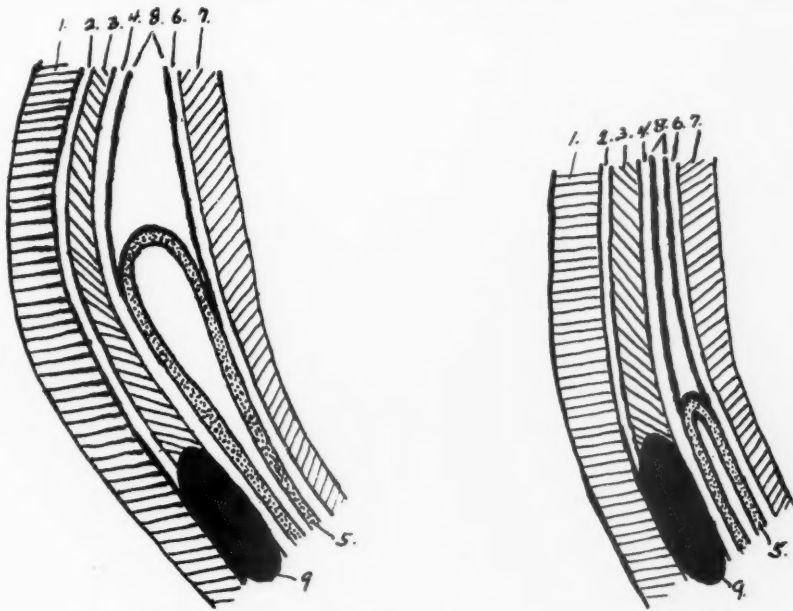


Fig. 2.—Longitudinal section, showing bladder distended and full.

Morbidity and Mortality.—There was no maternal mortality. Morbidity, exclusive of the first 2 postoperative days, occurred in 66 out of 100 cases. Fever ranged from 3 to 18 days with an average of $5\frac{1}{2}$ days. Causes for morbidity were: wound infections, endometritis, parametritis, pelvic thrombophlebitis (one case). The average hospital stay was 15 days; the shortest was 10 days, the longest was 92 days (case of pelvic thrombophlebitis). Many of the cases drained from the lower angle of the drain site for 2 to 4 weeks. Ten had definite wound infections.

Two infants were stillborn and 98 lived. One stillbirth occurred in a case of severe amnionitis and the presence of a fetal heart was ques-

tionable at the time of operation. The other one was in one of the cases of fetal distress and the presence of a fetal heart was reported just before the incision was made.

Discussion

Our experience with this operation is proof that a fairly large group can learn to do an extraperitoneal section successfully. Success depends upon an intelligent understanding of the anatomy of the pelvic fascia and its not infrequent variations. Many of the early failures with the extraperitoneal operation were due to a lack of clear understanding of the pelvic fascia, together with fear of bladder injuries. Throughout the history of extraperitoneal section there seems to have been an oft repeated pattern: first a small group of enthusiasts do the operation in a certain way; then other groups with very little experience and very little knowledge of the local anatomy involved, try to emulate the first group; they get into difficulties, and before long the operation is abandoned. In our own experience, the members of the group were able to do the procedure in shorter time and with less frequent peritoneal and bladder injuries as their experience increased and as their knowledge of the anatomy involved increased with it.

Our understanding of the anatomy of the pelvic fascia is such that we believe the bladder to lie or rest between several fascial planes or sheets rather than its being enclosed in a complete fascial envelope as has been described in most of the articles and texts. It is for this reason that the bladder cannot be completely dissected in a single plane out of its so-called fascial capsule from front to back, either superiorly or laterally. (See Figs. 1 and 2.) It is therefore necessary to incise the bladder fascia both anteriorly and posteriorly in order to reach the posterior bladder wall without injury. This dissection can be done either bluntly or with the knife, although we favor sharp dissection.

There are a number of points in the technique that we have found particularly helpful. First, the bladder should *not* be overdistended with fluid: a very thinned-out bladder wall due to overdistention, is difficult to dissect and easily perforated. Secondly, the lateral approach to the posterior vesical fascia should be made with the bladder empty and as low down as possible in order to avoid injury to a low dipping utero-vesical peritoneal fold. Thirdly, in the lateral dissection, the remaining anterior vesical fascia and the posterior vesical fascia are incised sharply until the glistening surface of the lower uterine segment comes into view. It is only by doing this that we can be certain to get posterior to the bladder and its posterior fascia without injuring the bladder wall, because the dissection will then take place between two definite fascial planes, instead of between bladder wall and posterior bladder fascia. Fourth, the peritoneum is dissected off the bladder dome by sharp dissection, hugging the bladder wall

rather than the peritoneum. Fifth, the pelvic fascia on the anterior lower uterine segment is incised transversely, thus mobilizing the uterovesical peritoneal fold which can then be pushed off the lower segment as far as desirable, giving us plenty of room for the incision. Sixth, the incision should be fairly large to avoid difficulty in extracting the baby and also to avoid extension in the uterine wall. Seventh, the head is most easily delivered with the hand after all retractors have been removed from the operative field. Eighth, all bladder injuries, small or large, must be repaired in 2 or more layers. Defects or thinned-out areas in the bladder wall should also be repaired in layers. All repaired bladders should have a retention catheter for at least 10 days. Ninth, the dissection of the bladder fascia can be carried out successfully even when the patient is not in labor, although it is usually easier with advanced labor. In this connection, we did the dissection successfully in a patient 27 weeks pregnant, not in labor, but found that extraction of the fetus was difficult due to the absence of a well-formed lower segment giving a very limited space for the uterine incision. Tenth, care should be exercised in retracting the peritoneal flap after its dissection from the bladder dome whether this be done by hand or with retractors. The retractor edges should not be sharp to avoid peritoneal injury.

Theoretically, the number of cesarean sections done on a large obstetric service, should definitely decrease, as borderline disproportion cases can be given a much more thorough test of labor. Similarly, cesarean section mortality should decrease because the danger of peritonitis is almost entirely eliminated. In our hospital, during the same period of four and a half years during which the 100 cases herein described were done, there were 444 other cesarean sections, with 4 deaths (one embolic, one anesthetic and two peritonitis deaths)—giving an overall cesarean section mortality rate of less than 0.74 per cent: this is much less than any other similar series of 544 cases at our hospital and also much less than our previously reported cesarean section death rate. We feel quite strongly that this marked reduction in our cesarean section mortality is in a large measure due to the extraperitoneal procedure.

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Discussion

DR. EDWARD G. WATERS.—The subject of sulfanilamide in actually and potentially infected transperitoneal operations is of great importance. Few of us who have had extended experience with sulfa drug therapy have any doubts as to its value and efficacy in handling infected patients. There can be no doubt about its value when used intraperitoneally. But since many patients with peritonitis who have had sulfanilamide used intraperitoneally still die of peritonitis, we do

not think that a transperitoneal operation with such semispecific therapy as is now available can compare with an extraperitoneal operation.

Since a forceps blade is smaller and more easily manipulated in the lower uterine segment than is a hand, we routinely use a forceps blade applying it in a lifting and prying manner like a vectis. We do not hesitate to do a version if there is difficulty with the head.

The lower uterine segment differs in character not only in patients who have been in labor but also in patients who have not been in labor. In general, the lower segment tends to thin out as labor progresses but we have seen some very thick segments in women who have had prolonged labors and we have seen extremely thin segments in women who have had no labor whatsoever. The character of the physiologic prelabor contractions of the uterus, especially in the last two months of pregnancy, exerts a marked effect on the lower uterine segment.

The cesarean incidence in my practice has dropped from nearly 4 per cent to 2.4 per cent in the last several years since we have more widely used extraperitoneal sections. We have delivered many patients vaginally, who previously would have had cesarean sections, by giving them an adequate test of labor with the possibility of an extraperitoneal section held in reserve.

The mortality of all our sections was 1.18 per cent. In the last eleven years we have had 21 section deaths in 1,771 cases. In the lower segment operations, there were 12 deaths or 1.06 per cent. In the extraperitoneal operations, there were 3 deaths or 0.83 per cent. In the 163 cases done by the Latzko technique, we had 2 deaths or 1.2 per cent. In over 208 cases done by the technique described here this evening there was one death, a mortality rate of 0.48 per cent. Thus there is actually a lowered mortality in potentially and actually infected cases, where by all reasoning one might expect it to be much higher. There can be no disputing the safety of an operation where a recognizedly worse risk still has a much better chance than the clean risk patient.

DR. MERVYN V. ARMSTRONG.—I would like to ask Dr. Waters if he can tell us how his cases could be divided into the necessary and the purely elective variety. I am interested to know the cause of the death in his one fatal case.

DR. WILLIAM F. NELMS.—I would like to inquire of Dr. Waters whether he has had occasion to do this operation a second time on the same patient and if so, whether he found great difficulty in exposing the lower uterine segment because of adhesions.

DR. EDWARD G. WATERS.—I have operated upon ten patients who had previous extraperitoneal sections. Obviously, an obstetric risk sufficiently bad to require an extraperitoneal operation the first time should not be left long in a subsequent labor. In the majority of the patients it was possible to operate extraperitoneally a second time, but in two patients it was not possible to do so. These patients had extensive cellulitis, marked scar formation, and the tissue was too adherent to separate. Both were converted into transperitoneal exclusion operations.

I cannot tell offhand how many of those 235 cases were necessary and how many were purely elective. On my own private cases I think possibly eight out of ten cesarean sections are extraperitoneal operations, just to demonstrate the technique. These patients make a satisfactory recovery after operation for they have had no peritoneal handling and no shock is induced. None die from pelvic cellulitis, when drained.

DR. ISIDORE DAICHMAN.—Dr. Waters brings up the question of extraperitoneal section with sulfanilamide versus transperitoneal section with sulfanilamide. At the present time there can be no question that the former procedure

is preferable, and is in fact the procedure that we frequently follow. However, we must be open minded about the possible eventual efficiency of chemotherapy. It is not at all impossible that chemotherapy may eventually completely replace the need for the extraperitoneal procedure.

From our experience with the supravescical extraperitoneal procedure, we feel that while each organ has its own intrinsic fascia, it also rests or "slides" between distinct fascial planes or sheets of the transversalis fascia, which, in the pelvis, splits to allow each of the organs to rest between clearly defined fascial layers. It is by working between these layers that the dissection can be accomplished without injury to the organs.

There is no question that clinically these patients run a much smoother post-operative course than they do after a transperitoneal approach. Abdominal distention occurs infrequently, and when it does occur, it can be faced with the assurance that we are not dealing with a peritonitis since the peritoneal cavity has not been invaded.

One cannot fail to be impressed by the marked reduction in our cesarean section mortality during the period of time covered by this report. Dr. Waters' figures are likewise impressive. There can be no doubt that a large measure of this is due to the use of the extraperitoneal procedure in those cases that would normally carry the highest operative risk. Furthermore, our experience indicates that the technique can be successfully mastered by any group of competent obstetric operators; that the complications are not formidable enough to prevent a group from overcoming them. Moreover, the operating time and incidence of complications will diminish considerably as experience with the operation increases.

PAIN THRESHOLD IN DYSMENORRHEA

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WHILE many interesting theories have been advanced as to the mechanism giving rise to dysmenorrhea, no study has been made of the difference in pain threshold between dysmenorrheics and non-dysmenorrheics.

The question arises as to whether dysmenorrheic patients actually receive more intense pain stimuli than do nondysmenorrheics, or whether they are merely more sensitive to pain than their more fortunate sisters. It would also be worth while to determine whether or not the two groups of women differ in sensitivity to pain after they have reached the menopause. Furthermore, how do males react to pain in comparison with normal, dysmenorrheic and postmenopausal females?

A lowering of the pain threshold in dysmenorrheics, as compared to normal women, has been suggested by many authors, but up to the present, experimental evidence to substantiate this hypothesis has been lacking. Studies on pain threshold have, however, been carried out on normal persons, as well as on psychoneurotic, hypothyroid, hypo- and hypersensitive individuals. In normal men and women, pain sensitivity, as measured by reaction to thermal stimulation, has been found to be relatively stable and uniform, both in the same subject¹ and in different subjects.² It also appears to be independent of age, sex, lack of sleep, or emotional factors.² More recently, however, considerable variation in pain threshold has been reported in a group of college women tested by an electric method.³ No explanation for the variability was offered.

Both thermal and electric methods, as employed by these investigators and by others,⁴ were considered impractical for the present study, since these procedures require too much time and equipment. A simple mechanical test had been devised by Libman⁵ who measured pain threshold by pressing firmly against the styloid process of the mastoid bone. The disadvantage of this method, however, was that the amount of pressure had to be gauged by the investigator; the results, purely qualitative, were therefore subject to considerable error because of the personal factor involved. Hollander⁶ also induced pain by mechanical means, using a grater attached to a blood pressure cuff; this method was employed in a small series of experiments by the present author, but was discarded because of the cumbersomeness of the apparatus. It is interesting that the figures obtained by Hollander's technique agree with those of the larger series reported in the present paper in which pain was also induced by pressure, with the sensimeter.

Procedure and Material

The sensimeter was employed in the present study because it gives accurate objective results and can be used conveniently anywhere with a minimum expenditure of time. This instrument has been adapted by Pelner⁷ from the Geneva Lens Measure by moving the fixed points 7 mm. apart. The salient feature of the sensimeter is a central movable point which is attached to a hand on a watch dial. The tests were made on the proximal phalanx of the thumb which was held horizontally while the distal phalanx was held at right angles to it. The



Fig. 1.—Sensimeter.

sensimeter was rested upon the proximal phalanx, and the dial number noted which registered the weight of the instrument. Pressure was then applied until the subject drew away or winced; at this instant the corresponding number on the dial was read. The figure registered on the dial before the pressure was exerted was subtracted from the second reading, and the difference was recorded. This procedure was then repeated on the other thumb. The mean of the two values represents the subject's pain sensitivity.

In this study the average pain threshold of 100 dysmenorrheic women was compared with that of 100 nondysmenorrheics, 100 women past the menopause,* and 100 male subjects. The dysmenorrheic group consisted of 50 individuals with so-called *primary* (essential, "intrinsic") dysmenorrhea, and 50 with *secondary* (acquired, "extrinsic") dysmenorrhea. One-half of the postmenopausal group was composed of women who had gone through the physiologic change of life, and the remaining half consisted of those in whom the menopause had

*In the postmenopausal group, the time interval since the last menstrual period ranged from two months to twenty-five years.

resulted from surgery. Furthermore, each of these two subgroups was equally divided into women who had had dysmenorrhea and those who had been free of pain with the menses.

Results

Table I shows the dysmenorrheic group to have a lower pain threshold than any of the other three groups tested; i.e., 12.2 for the dysmenorrheics, as compared to 14.9 for nondysmenorrheics; 15.2 for postmenopausal women; and 14.6 for males. The average of all three groups of women was 14.1, and the average of all four groups of subjects studied was 14.2. Thus the dysmenorrheic group average was 2.7 units below that of the nondysmenorrheic group, 1.9 units less than the average of the three groups of women, and 2.0 units less than the average of all four groups of subjects tested.

TABLE I. PAIN THRESHOLD IN FOUR GROUPS OF HUMAN SUBJECTS AS MEASURED BY THE SENSIMETER

GROUP	NO. OF CASES	AVERAGE PAIN THRESHOLD MEAN OF READINGS FROM RIGHT AND LEFT THUMB (SENSIMETER UNITS)	
I. Dysmenorrheic	100		12.2
(a) Primary	50		11.4
(b) Secondary	50		12.9
II. Nondysmenorrheic	100		14.9
III. Postmenopausal	100		15.2
(a) Surgical	50		15.2
1. Had dysmenorrhea	25		14.7
2. Had no dysmenorrhea	25		15.6
(b) Physiologic	50		15.3
1. Had dysmenorrhea	25		14.4
2. Had no dysmenorrhea	25		16.2
IV. Male	100		14.6
All women	300		14.1
All subjects	400		14.2

Patients suffering from the primary type of dysmenorrhea showed the highest sensitivity of any group or subgroup in the entire series studied: a threshold of 11.4, as compared to 12.9, obtained in the group of those afflicted with the secondary type of dysmenorrhea.

The highest threshold, i.e., the lowest sensitivity, of all four groups, on the other hand, was recorded among the postmenopausal women, 15.2. No explanation is offered for this finding. The average pain threshold of the surgical menopausal subjects was only 0.1 unit less than that of women who had gone through the natural menopause, 15.2 and 15.3, respectively. However, it is of interest to note that individuals who had had dysmenorrhea earlier in life showed a decidedly lower threshold than those who had experienced no pain with their periods. This is true of both major groups of menopausal subjects, e.g., 14.7 (surgical menopause), and 14.4 (physiologic meno-

pause), in those with a history of dysmenorrhea, as against 15.6 (surgical menopause), and 16.2 (physiologic menopause), in women who had been free of pain at catamenia.

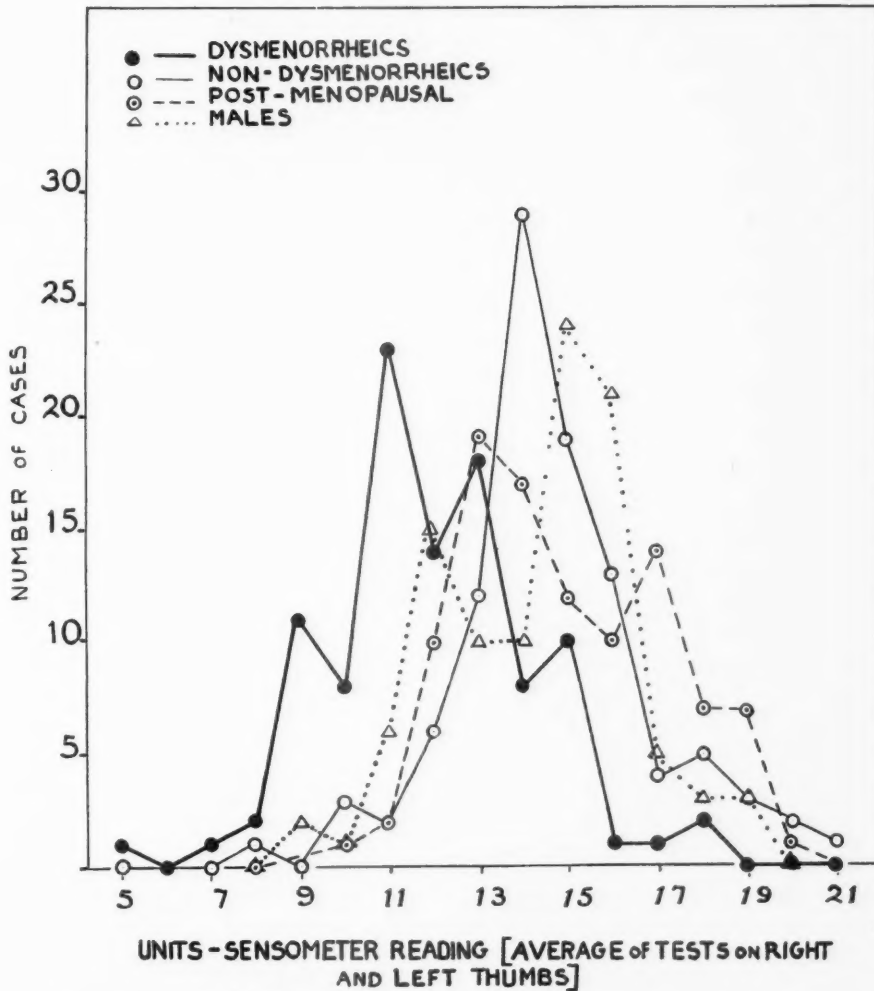


Fig. 2.—Curves showing the preponderance of dysmenorrheics in the low threshold area and their relative infrequency in the high threshold areas as compared to other individuals.

The pain threshold of the male subjects was 14.6, only very slightly higher than that of the average of the three groups of women (14.1). Likewise, the reaction to pain of men did not differ significantly from that of normal and postmenopausal women (14.9 and 15.2, respectively). Thus, if one excludes the dysmenorrheics, the group in which sensitivity to pain was markedly greater than in the other groups of women studied, it appears that in normal subjects pain threshold is in general independent of sex, an observation previously reported by Schumacher and his co-workers.²

Since deductions based on average figures alone may often lead to erroneous conclusions, frequency distribution curves were plotted for the four groups of subjects tested (Fig. 2). These show the variations within each group. While a mathematical analysis of the results has not been attempted, comparison of the modal values in the four groups confirms the conclusion derived from average figures as to the relatively high degree of pain sensitivity of dysmenorrheics.

It should be pointed out that in comparing the reactions of normal and of dysmenorrheic women to pressure stimuli on the thumb, as in the present investigation, the question might be raised as to the validity of making inferences from a study of pain elicited on the surface of the body to pain that would be experienced by dysmenorrheic women at the time of menstruation. However, recent experimental evidence indicates that a parallelism between superficial and deep pain does exist, and that "inferences drawn from the studies of superficial pain are valid for deep pain."⁸

Summary and Conclusions

1. The hypothesis, often suggested, that dysmenorrheics have a lower pain threshold than normal women, has been substantiated by a study of 400 subjects, comprising 100 dysmenorrheics, 100 nondysmenorrheics, 100 women past the menopause, and 100 males.

2. The average pain threshold of the dysmenorrheic group was lower than that of any of the other three groups of subjects tested. Women suffering from the primary type of dysmenorrhea showed a higher sensitivity than those afflicted with the secondary type. When frequency distribution curves were plotted for the four groups of subjects studied, a comparison of the modal values confirmed the conclusion derived from average figures as to the relatively high degree of pain sensitivity of dysmenorrheics.

3. The highest average pain threshold of any group was noted in women past the menopause. Those who had a history of dysmenorrhea showed a lower threshold than those who had had painless periods.

4. If one excludes the group of highly sensitive women, the dysmenorrheics, pain threshold does not appear to be markedly affected by sex.

5. Since a study of pain sensitivity within the postmenopausal group indicates that the lowered pain threshold of the dysmenorrheic is retained even past the climacteric, there apparently exists in the constitution of the dysmenorrheic woman an intrinsic factor that renders her more susceptible to pain than the nondysmenorrheic individual.

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490 POST STREET

DIMETHYL-ETHER STILBESTROL IN THE MENOPAUSE AND FOR THE SUPPRESSION OF LACTATION

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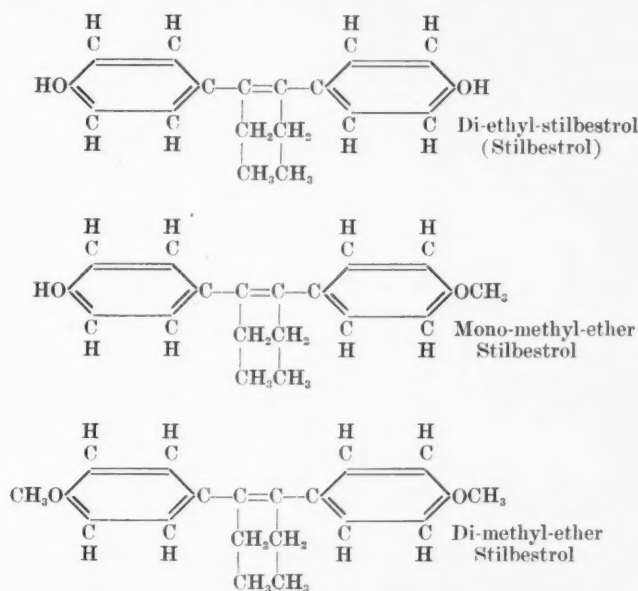
DIMETHYLSTILBESTROL, usually referred to as stilbestrol, has not proved wholly satisfactory in the therapy of either the menopause or in the suppression of lactation. In the former, toxic reactions ranging from 10 per cent to 50 per cent according to various authors, and varying from simple nausea and vomiting to exfoliative dermatitis and angioneurotic edema, are the chief objections. In the suppression of lactation, the author found stilbestrol adequate during the parturient's stay in the hospital. However, reports from patients two weeks' post partum revealed a large percentage with reingorgement of the breasts. Further added treatment with stilbestrol, in these cases, resulted in an alarmingly profuse first menstrual period. This added data necessitates revision of the value of the results obtained and reported previously by this author.

During the last two years, numerous articles have been published dealing with a host of new synthetic estromimetic agents, the majority of them derivatives of stilbestrol. These are the fatty acid salts (dipalmitate, dipropionate and benzoate), dihydrostilbestrol (hexestrol), and the methyl ethers. The greater number of these reports are comparison studies of dosage, therapeutic efficacy, and toxicity between stilbestrol and several of its salts. Although some of these compounds are less toxic than stilbestrol, it must be emphasized that none of these are entirely free from "unpleasant sequelae." It is an accepted fact at present that by increasing the length of the side chain of stilbestrol, or by stearification with the aliphatic acids, there is a decrease in potency and toxicity, for the same dosage level, but a more prolonged estrus effect. However, the ideal synthetic estromimetic, that is, potent and free from all toxicity, has not as yet been described.

The case for the methyl ethers is aptly summarized by Teague, as follows: "A few papers have appeared recently concerning monomethyl stilbestrol. This ether derivative presumably becomes demethylated in the body, liberating free diethylstilbestrol. It seems to offer the advantage over free diethylstilbestrol of producing fewer side-actions in the effective dose range."

The above paragraph stimulated further investigation in the chemistry and pharmacology of the methyl ethers of stilbestrol. Notwithstanding the excellent reported results with monomethyl ether stilbestrol, the author felt that the dimethyl ether stilbestrol, because of

its chemical configuration, might be still more efficacious. The following structural formulas, of stilbestrol and its mono- and dimethyl ether derivatives, show the differences between the three chemicals, i.e., the substitution of one methyl radical for each hydroxyl group, making either a mono- or a dimethyl ether out of the original diphenol.



In the laboratory, great difficulty is experienced in the demethylation of the methyl ethers, by chemical means. Furthermore, it is believed that since methyl radicals are ethers, they would also be more stable to oxidation in the organism, resulting in more prolonged and uniform activity, depending upon the rate of demethylation and utilization. However, there is no authoritative statement on the relative rapidity of absorption and oxidation, of the methyl and ethyl radicals, permitting prognostication as to clinical results of therapy with these agents. Nevertheless, the difficult chemical demethylation, in vitro as well as in the organism, offers a reasonable pharmacologic explanation of the clinical results herewith obtained and reported.

Menopause

This group of cases studied represents 22 from the gynecologic clinic of Dr. M. N. Hyams at the N. Y. Post-Graduate Hospital and 27 from the author's private practice, treated and observed for the past 18 months. This mixed group of women from all social strata makes possible the elimination of psychic factors in improvement, prevalent in the therapy of the menopause, particularly in private patients. Every patient originally applied for relief from "change of life." All complained of flushes, sufficiently frequent during the day to interfere

with the usual routine and severe enough to arouse them from sleep. One patient suffered from flushes occurring every ten minutes and threatened suicide unless relieved. Associated with the vasomotor symptoms of flushes, chills, and sweats were symptoms referable to the nervous system, such as melancholia and irritability, in some cases.

The sole method of assay used was the patient's reactions, as advocated by Greenhill. Liberation from symptoms meant successful therapy and absence of side-actions indicated freedom of toxicity from the drug.

Method.—Dimethyl ether stilbestrol, 30 mg. dissolved in 1 c.c. of sesame oil, was injected intramuscularly and repeated weekly until all symptoms subsided. One patient received 60 mg., 3 were given 75 mg., and one required 120 mg. With the exception of these five, the other 44 cases received 90 mg. We can therefore assume the average dose necessary for complete relief to be 90 mg. divided into three weekly doses of 30 mg. The patient was then instructed to return at monthly intervals for observation. No supplementary oral treatment of any kind was given. When the symptoms recurred, a similar course of treatment was instituted. The total number of symptomless days was computed and served as the index of the efficacy of the drug, in each individual case.

Results.—The results obtained with dimethyl ether stilbestrol more than fulfilled all expectations, as to potency, duration of effects, and absence of toxicity. Table I is a résumé of these findings.

TABLE I

TYPE OF MENOPAUSE	CLINIC CASES	AVERAGE NUMBER DAYS SYMPTOM-FREE	PRIVATE CASES	AVERAGE NUMBER DAYS SYMPTOM-FREE
Natural	17	144	18	156
Surgical	5	112	9	121
Total	22	132	27	144
Toxic Reactions	0		0	

It will be noted that the average number of days, free from any symptoms referable to the menopausal state, are 132 for clinic cases and 144 for the private, with a mean average of 138 days for the entire group. Noteworthy is the inexplicable shorter duration of relief in the surgical menopause cases as compared to those in the natural menopause, i.e., 112 against 144 days in the clinic group and 121 against 156, in private cases. The author is unable to find any record of this observation, in the literature, and will appreciate correspondence, either confirming or denying the constancy of this finding. The one most significant fact is the total absence of any toxic reactions. Careful questioning failed to elicit an admission of even simple nausea. The prolonged potent effects and freedom from any toxic side-actions stamp dimethyl ether stilbesterol as the possible ideal estromimetic.

Suppression of Lactation

This part of the study was carried out at the Menorah Maternity Division of the Beth-El Hospital, Brooklyn, with the cooperation of the obstetric staff.

It is apparent, because of its long period of latent activity, that dimethyl ether stilbestrol, per se, could not be of any value in suppression of lactation. However, in combination with stilbestrol a mixture is obtained in which both drugs are supplemental, in much the same way as obstetric pituitrin and ergotrate. The stilbestrol, a quickly-acting suppressant, makes possible the symptom-free period until the slower acting dimethyl ether stilbestrol exerts its prolonged effects, thereby diminishing the secondary reingorgement, so frequent with stilbestrol alone. In this study, 15 mg. of stilbestrol and dimethyl ether stilbestrol, dissolved in 1 c.c. of sesame oil, were administered intramuscularly and repeated in 48 hours.

A total of 269 cases were treated and observed in the manner outlined. Of these, 245 received but the two injections and 24 required a third one, administered usually on the day of discharge from the hospital. Four cases were complete failures, judged by painful and engorged breasts, requiring some other form of relief. These patients may have been refractory to these estrogens. Obviously, the problem of reingorgement is of paramount importance in a study such as this, and every effort was made to ascertain the total number of cases, reporting any degree of reingorgement. Included in this group are cases that required no further therapy or relief. Yet their inclusion was thought advisable, to rule out all element of doubt as to the therapeutic efficacy of this mixture. Approximately 11 per cent suffered with reingorgement. This is probably due to improper supervision. The author believes that a third dose of the mixture would have prevented this complication, for in the 24 cases receiving three injections there was no incidence of reingorgement.

TABLE II

NUMBER	CASES	WITH RE- INGORGE- MENT	TOTAL FAILURES	DOSAGE
With 2 doses	245	29	0	30 mg. stilbestrol 30 mg. dimethyl ether stilbestrol
With 3 doses	24	0	4	45 mg. stilbestrol 45 mg. dimethyl ether stilbestrol
Total	269	29	4	

Delay in onset of menstruation occurred in about 30 per cent of the cases—in some for as long as two months past the usually expected time. This fact serves not only to explain the mechanism of suppression of lactation, by inhibiting the anterior pituitary gland in its production of prolactin, but is a direct indication of the pharmacologic activity of the estrogens employed. One case of profuse bleeding, four weeks post partum, necessitated a curettage, which revealed a cystic glandular hyperplasia of the endometrium.

As a whole, these results may be regarded as satisfactory. However, it is not the intention to allow the formula of the mixture and the

dosage to remain static. This investigator is not aware of any similar or previous study, with a mixture of estrogens, in the suppression of lactation, and hopes that this may serve as a stimulus to further studies. Improvement in results will undoubtedly be attained by continuous experimentation, for the optimum mixture and method of administration.

Summary

1. In the menopause, dimethyl ether stilbestrol gives the following results:

- a. Absence of any toxic reactions,
- b. Freedom from symptoms referable to the menopause for an average period of 138 days or approximately four and one-half months, and
- c. Patients with surgical menopause have a shorter duration of relief than those in a natural menopause.

2. In the suppression of lactation, in a mixture with stilbestrol,

- a. The incidence of reingorgement was reduced,
- b. The onset of the first menstrual period was delayed, in 30 per cent of the cases.

The author wishes to express his appreciation to Dr. M. N. Hyams for his permission to utilize the clinic patients in this study; to Drs. Halperin, Levine, and Koplowitz for their generous cooperation and permission to treat their private and service obstetric cases, for the suppression of lactation, thus making this study possible.

The material used was supplied by W. F. Straub & Company, Chicago, Ill. The dimethylether stilbestrol is known under the name of Synthil A. The combination of estrogens used in the study of suppression of lactation was also prepared by the same company. The author wishes to thank this company for its cooperation and for the materials supplied.

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PROLONGATION OF PREGNANCY AND EXCESSIVE FETAL DEVELOPMENT FOLLOWING ADMINISTRATION OF CORPUS LUTEUM EXTRACT IN THE TREATMENT OF THREATENED ABORTION

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SNYDER¹ administered extract of pregnancy urine to rabbits late in gestation. Fresh corpora lutea resulted, the onset of parturition was delayed, and the fetuses developed to excessive size.

Heckel and Allen² treated rabbits late in pregnancy with estrogenic substance. The fetuses died shortly after the maternal treatment, but nevertheless the onset of parturition also was delayed.

Koff and Davis³ administered corpus luteum extract to rabbits late in pregnancy. This treatment delayed the onset of parturition, and the resulting fetuses showed evidence of postmaturity by their unusual size and state of development.

Snyder considered that the prolongation of the pregnancies of his animals was due to the activity of the experimentally produced corpora lutea. Heckel and Allen assumed that the same phenomena in their animals resulted from the fact that the estrogenic substance maintained the functional activity of existing corpora lutea. Koff and Davis concluded that the corpus luteum played a definite role in controlling the gestations of their rabbits.

The present report concerns a patient who received a large amount of corpus luteum extract during the first half of her pregnancy, which was administered in order to control a threatened abortion. Her pregnancy persisted for 44 weeks and her infant was unusually large at birth.

Case Report

Mrs. A. S., white, aged 31, had had her first pregnancy terminate by a spontaneous abortion in July, 1942. Normal menstruation, which had always been regular, became re-established immediately. Her last normal period began January 3, 1943. Nausea was experienced for the first time on January 25. Uterine cramps began on February 6. Slight uterine bleeding occurred on February 21 and recurred several times between that date and March 21 when it appeared for the last time. Uterine cramps of variable strength and duration recurred frequently at irregular periods daily from their onset on February 6 until June 6, at which time they ceased. During practically this entire time the patient remained in bed.

For the 4 months while uterine cramps were taking place, the patient took orally an average of 14 grains of corpus luteum extract* daily, consuming in this period some 1,500 grains of the material.

*Corpus luteum was administered orally in the form of Lutein (Hynson, Wescott and Dunning Co.). According to the manufacturer, each 2-grain tablet represents approximately 8 grains of fresh corpus luteum of the sow, freed as far as practical from other ovarian tissue, and dried in a vacuum. The patient took an average of seven tablets daily, and more on days when cramps were unusually severe or frequent.

Fetal activity was experienced for the first time on May 16, during the twentieth week of gestation. On the basis of her menstrual history and other findings, the expected date of her confinement was computed as being October 10.

At the end of the second and third weeks after the expected date of confinement the patient took castor oil with the hope of starting labor, but this was without any effect upon her uterine motility. On November 6, which was 26 days after the expected date of confinement, labor began spontaneously. After 36 hours of uterine contractions of only fair strength the fetal head had failed to engage, and the cervix was dilated only 4 centimeters. As a result, the patient was delivered by cesarean section, the infant being found to weigh 4,990 grams (11 pounds).

Comment

Certain questions arise in connection with this case. Was the pregnancy actually prolonged? In support of a positive answer to this question are the following facts: The mother of the infant was an intelligent college graduate. Her menstrual history was always regular. The date of her last menstrual period was known accurately and this period was normal. She experienced nausea within four weeks of her last period. Life was felt during the twentieth week of gestation. Castor oil failed to elicit a uterine reaction on two different occasions after the expected date of her confinement. The patient kept a daily record of all signs and symptoms until all evidence of threatened abortion ceased.

With respect to the size of the infant, the following facts are of interest: The mother weighed only 140 pounds before conception, and the father weighed 160 pounds, neither of them being of unusually large size. The infant was the first born; large infants usually are the later born in a family.

No information was available regarding the biologic potency of the corpus luteum extract. The patient, however, failed to abort in spite of the fact that cramps persisted for 4 months, and she did so previously at a time when she received no treatment with corpus luteum extract.

No similar experience has been unearthed in the literature, and this may have been due to the fact that probably no other patient received so large an amount of the drug over such a long period of her pregnancy.

If one assumes that this pregnancy was prolonged as a result of the administration of corpus luteum extract, its action remains to be explained. Two possibilities can be considered: Either the drug remained potent in the body, or its presence early in pregnancy spared the patient's own corpus luteum to be effective later in pregnancy. There may be no correlation between the treatment of this patient, and the length of her gestation and the large size of her child, but the above-mentioned experimental evidence would seem to be highly confirmative.

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SPINAL ANESTHESIA TO FAVOR RAPID DILATATION OF THE CERVIX IN OBSTETRIC EMERGENCIES

Preliminary Report

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OCCASIONS arise in obstetric practice where immediate delivery is imperative. These occasions fortunately are few, but nevertheless if poor results and tragedy are to be avoided, they must be treated by a technique that will be both effective and safe. Ordinarily when confronted by a case of prolapsed umbilical cord, irregular fetal heart, etc., our most important guide to treatment is the condition of the cervix. In the absence of disproportion, given a soft and dilatable cervix, the accoucheur usually completes the dilatation manually and then effects delivery by either forceps, internal podalic version or breech extraction depending on the presentation, position, degree of engagement and his own preference. Should a similar set of conditions present themselves in a case where the cervix is thick and leathery and not dilatable, the case is usually treated by attempts at cord replacement, at best a procedure that yields poor results, or by Dührssen's incisions of the cervix, or perhaps by cesarean section. In a great many cases the fetus is abandoned, the labor being conducted solely in the interest of the mother. Few obstetricians fortunately have the temerity to forcibly dilate the cervix and then effect delivery.

In the types of cases under discussion, I have employed spinal anesthesia with highly satisfactory results.

Delmas¹ in 1929 reported delivering women before the onset of labor by manually dilating the cervix and performing internal podalic version. Anesthesia was induced by the spinal route. This procedure at that time and even now impresses me as unnecessarily meddlesome and radical. However, given the proper indication this procedure can prove invaluable. Within the last few months, I have delivered a number of women by this technique, the results and conclusions of which will be reported in a subsequent paper by the author and Dr. Joseph Feibush who administered the anesthetics and worked out important details such as the preferred anesthetic agent, the optimum dosage, etc., and has also made careful and important observations of physical and mental reactions of patients during and following anesthesia.

The following cases illustrate both the indications and the technique employed.

My first delivery by this method was in 1939.

CASE 1.—Mrs. M. F., aged 27, gravida v. All the previous pregnancies ended in stillbirths in the seventh month of pregnancy. She was told that all of her pregnancies were complicated by toxemia. On the present admission to the hospital, the urine showed four plus albumin and the blood pressure was 132/82. Labor was induced medically three days after admission by castor oil and injections of Pitocin. The membranes ruptured that day but there were no labor pains. Leakage of amniotic fluid continued and at the end of two weeks there were still no appreciable labor pains. The cervix at this time was two fingers dilated and a Voorhees' bag was inserted. The bag was ineffective for despite its presence plus the administration of oxytocics, there were only irregular uterine contractions. Two days after the insertion of the bag, the patient had a chill and the temperature rose to over 103 degrees F. Her condition appeared desperate and immediate delivery was deemed imperative. The cervix at this time was three and one-half fingers dilated but thick. Inhalation anesthesia was considered inadvisable and delivery by the Delmas' technique was decided on.

Under spinal anesthesia, employing 1.3 c.c. tropococaine, the Voorhees' bag was removed. At the junction of the cervix and the lower uterine segment there was a marked contraction. This was dilated manually for some time, and when it disappeared podalic version was performed. The child showed several small areas of maceration and there was a loose knot in the umbilical cord. The placenta was expelled by the Credé maneuver. The entire procedure took thirty minutes. The relaxation was good, the respirations were regular and there was no vomiting. The patient had a stormy convalescence but left the hospital in good condition.

CASE 2.—Mrs. A. B., aged 36, gravida iii, para o. The last menstrual period was on September 23, and expected date of delivery June 30. I saw her with her family doctor on July 13, the reason for the consultation being an irregular fetal heart rate. The rate varied between 100 and 180 per minute. The fetus appeared to be average size and the pelvis ample. The cervical canal was obliterated and the cervix admitted the tip of a finger and was soft.

Under spinal anesthesia employing 150 mg. of procaine the cervix was easily dilated manually to full dilatation in seven minutes and a podalic version was performed. A normal living infant was easily delivered. The placenta was delivered a few minutes later by simple expression. Small bilateral cervical lacerations were repaired as was a right lateral episiotomy. Mother and baby left the hospital in ten days in good condition.

CASE 3.—Mrs. J. S., aged 28, gravida i, para o. Last menstrual period December 23, expected date of delivery September 30, 1943.

Patient went into labor on September 21, and after twelve hours of labor, the fetal heart became very irregular and violent fetal movements were observed. The fetus was evidently in distress and immediate delivery was deemed necessary.

Under 80 mg. of neocaine the cervix was found to be thick and one finger dilated. The position was right occipitoposterior and the head unengaged but engageable. Full cervical dilatation was easily obtained by manual dilatation. The occiput was then rotated to left occipito-anterior by a manual maneuver previously described by the author.²⁻³ Axis traction forceps were then applied cephalically and a normal living

infant delivered. Moderate-sized cervical tears were easily repaired as was a right lateral episiotomy. The placenta was delivered by simple expression.

Mother and baby left the hospital on the ninth post-partum day in good condition.

CASE 4.—Mrs. B. F., aged 27, gravida ii, para i. Patient came from Arkansas and was very anxious to get back to her family. The menstrual history was indefinite, but judging from the size of her abdomen and the day she said she felt life, I deemed her at term on August 12, and proceeded to induce labor by rupturing the membranes. The cervical canal was obliterated and the cervical os was thick and admitted two fingers. The cord prolapsed into the vagina immediately after the rupture of the membranes and the pulsations were weak. Immediate delivery was considered urgent and accordingly a podalic version was performed under spinal anesthesia, employing 100 mg. of procaine and a living normal child was delivered despite the fact that the cord was not pulsating at birth. The implantation of the placenta was low and this factor probably explains the prolapse of the cord. There were no cervical or perineal tears and the placenta was expelled in a few minutes by simple expression.

Mother and baby left the hospital on the ninth post-partum day in good condition.

CASE 5.—Mrs. C. M., aged 22, gravida i, para o. Patient was admitted to the hospital because of pregnancy complicated by subacute bacterial endocarditis.

Her expected date of delivery was on August 30, 1943. She went into labor on July 3, and for fear of producing depression and asphyxia in the premature child no sedation was given the mother. Soon after initiation, labor became strong and the patient was uncooperative and "fagging" herself out.

The cervix was then two fingers dilated. One hundred mg. of procaine were administered by the spinal route and within one minute manual dilatation attained full cervical dilatation. The membranes were then ruptured artificially and a living premature child weighing 3 pounds and 5 ounces was delivered by low forceps.

The patient stood the ordeal well and was very grateful for the immediate relief from pain accorded by the spinal anesthesia. On the tenth post-partum day she was transferred to the medical service and the child left the hospital in good condition on the forty-second day. The mother is still alive at the time of this writing.

Discussion

It can be demonstrated pharmacologically and certainly clinically that spinal anesthesia relaxes the cervical muscles so that the cervix can be easily dilated, and at the same time, it causes contraction of the corporeal muscles. This latter action greatly limits the blood loss.

While it is true that the cervix can be manually dilated under general anesthesia, nevertheless the advantages gained by employing spinal anesthesia make it the anesthetic of choice in the type of cases under consideration. Under spinal anesthesia, the dilatation of the cervix can be more easily performed, the child practically always cries

spontaneously, obviating the need for resuscitation and the blood loss is usually far less than under general anesthesia.

Due to the fact that every case requires delivery by a major obstetric procedure, it follows that this technique should be employed only by thoroughly experienced obstetricians for otherwise the results will not only be unsatisfactory but in many cases truly tragic.

Summary

The employment of spinal anesthesia in obstetric patients in whom immediate delivery is indicated is advocated and discussed. Five illustrative cases are described.

Conclusions

In instances where haste is indicated and cephalopelvic disproportion does not exist, delivery under spinal anesthesia is both feasible and very satisfactory.

Every case subjected to spinal anesthesia requires mastery of obstetric operative procedures, therefore patients anesthetized by the spinal route should be delivered by thoroughly trained and experienced obstetricians.

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1882 GRAND CONCOURSE

PREGNANCY AT TERM IN PROLAPSED UTERUS WITH PROLAPSE OF CORD*

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PROLAPSE of the uterus at or near term is rare. In the Bronx Hospital from January 1, 1938, to November 1, 1943, this case is the only one in 15,696 deliveries. Keettel¹ had one case in 13,000 deliveries in a period of over 14 years. From another hospital he was able to report another case which occurred in 2,000 deliveries over a period of 10 years. This led him to analyze 170 reported cases, 137 of which were collected before 1901 by Franke, Seitz and Andrews. Palmer Findley³ added 10 more cases in 1911, and 23 other reports, including the three he reports, have appeared since then. Most of the cases that have gone to term showed only an elongated, hypertrophied and edematous cervix. Up to the seventh lunar month cases have been reported with complete procedentia, but with a full-term fetus this is hardly possible. Most of Keettel's analyzed cases occurred in multiparas.

The condition seems to have little effect on fertility and pregnancy occurred in spite of marked chronic endocervicitis. Early abortion (21 per cent) is relatively frequent. Findley advises plastic repair at this early stage without interruption of pregnancy. It was found that, because the uterus rose out of the pelvis after the fourth or fifth month of pregnancy, thus pulling the cervix into the vagina, there was less tendency to spontaneous abortion. Therefore, Franke and Seitz, in their earlier cases, recommended the use of a pessary until the uterus was enlarged and the cervix drawn upward. Andrews² feels the incidence of breech presentations was increased.

The operative incidence reported by Keettel was high. The most common method of delivery, outside of spontaneous deliveries (45.7 per cent), was the use of forceps (27.1 per cent), after Dührssen's incisions (29.3 per cent). Version and extraction (4.3 per cent), craniotomy (7.8 per cent), and cesarean section (one case of the Porro type) were used only occasionally. The fetal death rate was high (22.1 per cent). Maternal mortality was also high (6.3 per cent), nearly all due to sepsis.

The treatment of this condition was formerly radical, but has in recent years become conservative.

Case Reports

Mrs. D. L., aged 39, gravida v, para iv, came to the prenatal clinic for the first time on July 27, 1943. At this time she stated her last menstrual period was February 1, 1943, and her expected date of confinement was figured as November 8, 1943.

Her past medical and surgical history was negative. She had four children, the oldest eighteen and the youngest two years of age. Their birthweights were 8, 9, 9, and 7 pounds and 10 ounces, respectively.

*This case report was made available through the courtesy of Dr. Meyer Rosensohn, attending Obstetrician, Bronx Hospital, New York, N. Y.

†Presented at a meeting of the Section of Obstetrics and Gynecology of the New York Academy of Medicine, December 28, 1943.

Physical examination revealed the heart and lungs negative. The pelvic measurements were ample. The abdomen showed a five months' pregnancy, the height of the fundus above the symphysis being 21 cm. Vaginal examination revealed a cystocele, rectocele, and a first degree uterine prolapse. Urine and Wassermann tests taken at this time were negative.

The prenatal clinical course was uneventful with her blood pressure around 105 systolic and 60 diastolic.

According to her history, on the night of October 19, 1943, she felt something protruding from the vagina, but she went to bed, and did not enter the hospital until 10:35 A.M. of the following day. There were no edema and no pains. The abdomen revealed a pregnancy almost at term, breech presenting, with the back to the right and anteriorly. No fetal heart sounds were heard. Projecting from the vagina for a considerable distance were the cervix and the uterus, and protruding from the cervix was a nonpulsating cord. In the delivery room, after sterile precautions, the protruding mass was redeposited into the vagina. At this time the cervix was dilated $1\frac{1}{2}$ fingers and a footling presentation was made out. That afternoon, when seen by the attending obstetrician, the temperature had risen to 102° F. Noting the absence of pulsation of the cord, and the length of time it had been prolapsed, no interference at this time was advised. Two grams of sulfadiazine were given immediately, followed by one gram every four hours. Two ounces of castor oil were also given, with the hope of inducing labor.

By 9:00 P.M. that evening, the patient was having moderate contractions, but because of her temperature 1,000 c.c. of 5 per cent glucose were given intravenously, and she was given sedatives. At 7:15 A.M. the following morning, after a $10\frac{1}{4}$ -hour labor, the patient delivered a stillborn breech, R.S.A., female, weighing 7 pounds. There was no laceration. Following the delivery the patient had a chill, and the temperature rose to 103.6° F., which dropped to normal by 4:00 P.M. that afternoon.

The laboratory examination showed urine: specific gravity 1.020, sugar and albumin negative, acetone 2 plus, diacetic acid 1 plus, occasional red blood cells, and 4 to 5 white blood cell per high power field. Blood count showed hemoglobin 92 per cent, red blood cells 4,230,000, white blood cells 23,100, polys 80 per cent, band forms 7 per cent, lymphocytes 13 per cent and toxic granulation of the neutrophils. Blood culture was sterile after 144 hours of incubation.

For the next few days the temperature fluctuated around 100° F., but was back to normal on the fifth day postpartum. Except for a slight cough, but with no signs in the chest, the puerperium was uneventful, and the patient was discharged on the tenth day post partum. She was sent to the gynecological clinic, to be later referred to the hospital for operation.

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1565 TOWNSEND AVENUE

**A CASE OF PSEUDOHERMAPHRODISMUS FEMINUS
EXTERNUS WITH UTERUS DIDELPHYS,
IMPERFORATE ANUS AND VAGINA**

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CONGENITAL malformations of the urogenital system are adequately described in most obstetric textbooks. The case presented is interesting because of the inability to determine the sex of the infant before death and the bizarre combination of anomalies which were found at autopsy.

Mrs. V. H., aged 19, primipara, was first seen in the prenatal clinic of the Station Hospital, April 16, 1942. Her last menses occurred Dec. 5, 1941, and the expected date of delivery was Sept. 12, 1942. Examination revealed the uterus enlarged to 20 weeks' gestation. The pelvic measurements were normal and the rest of the examination was essentially negative. The prenatal course was normal in every respect and patient went into labor Sept. 16, 1942. In 4 hours the baby was spontaneously delivered after a midline episiotomy. The puerperium was uneventful and the mother was discharged from the hospital on the tenth day. The baby weighed 8 pounds and cried at once.

Physical examination of the baby revealed congenital anomalies. The rectum was absent nor was there any dimple to show the presence of a blind pouch. The genitals were distinguished by two normal looking labia majora. There were no labia minora. The vaginal opening was absent nor was there any evidence of a hymen. The clitoris was hypertrophied to four times the normal size, resembling a penile organ. Just below it was a longitudinal urethral opening and below this was a small pendulous scrotal-appearing structure. Testes were not palpable here nor in the groin. The sex could not be determined definitely.

Course.—The baby outwardly appeared in good condition. Urine passed from the urethra. Occasionally gas was expelled through the same orifice. Seventeen hours after delivery, under local anesthesia, the perineum was explored surgically by Major T. R. Hannon, M. C., but no rectal pouch could be found. Thereupon a simple left-sided colostomy was performed by bringing a loop of sigmoid up through the lower left rectus muscle and suspending it in position with a glass rod under the intestinal loop. Twenty-four hours later the colostomy loop was opened by a live cautery and bowel function began through this opening. The baby took artificial feedings well and was discharged from the hospital on the tenth day in good condition, weighing 7 pounds 14 ounces.

On October 5, 1942, nine days after leaving the hospital, the baby was readmitted, acutely ill with a history of vomiting, fever, and increasing abdominal distention. For the past 24 hours no urine had been passed and the fecal drainage from the colostomy had almost ceased. Physical examination revealed an acutely ill infant with marked abdominal distention. There was a firm, fixed mass in the right lower quadrant, pressure on which caused urine to flow from the urethra. X-rays made after injection of skiodan into the loops of the colostomy failed to reveal any definite evidence of obstruction. X-rays of the genitourinary system with retrograde skiodan injection were

suggestive of a multicystic kidney on the left side. No kidney or ureter was visualized on the right side. The colostomy was irrigated with saline solution and profuse amount of fecal matter was discharged. The abdominal distention subsided. However, the urinary suppression continued, the baby became toxic, vomited persistently and died 36 hours after admission, 21 days after birth.

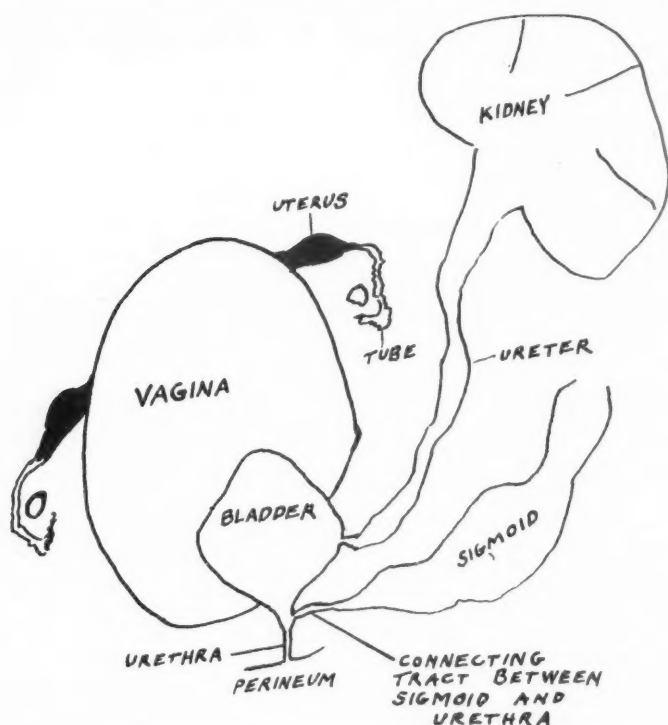


Fig. 1.—Diagrammatic representation of congenital anomalies.

Autopsy.—The following is an excerpt of a complete postmortem examination done by Captain George M. Hass, M. C.: Terminal pneumonia and the presence of a colostomy was noted. The rectum terminated in a narrow tract about 1 centimeter long and 3 millimeters in diameter which communicated with the posterior urethra. The right kidney and ureter were absent. The left kidney and ureter were dilated and showed evidence of recent infection. The bladder was normal except for absent right ureteral orifice. Posterior to the bladder was a large cyst about 15 centimeters in diameter, filled with foul smelling yellowish purulent material under tension. On each of the upper and lateral aspects of the cyst was a uterus, tube and ovary. Below, the cyst reached to about 1 centimeter from the skin of the perineum at the vulval region where the vaginal introitus should have been.

Final Diagnosis.—1. Acute pyelonephritis left kidney due to congenital connection between sigmoid colon and posterior urethra,

2. Hydronephrosis left kidney,

3. Uremia, terminal, and

4. Congenital anomalies: absence of right kidney and ureter; uterus didelphys; imperforate anus; imperforate vagina; pseudohydrocolpos; urethrosigmoid fistula; pseudohermaphroditism feminus externus.

TUBAL PREGNANCY IN A TUBERCULOUS FALLOPIAN TUBE

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THE coexistence of tuberculosis and ectopic gestation in the Fallopian tube appears to be a very rare occurrence. In 1939, Stevenson and Wharton¹ reviewed the literature of the subject and noted that exclusive of their own single case, only 8 cases had been previously reported. They believed that their case was the first proved case reported "from the English-speaking world." It was also the first case in the 47 years of the existence of the gynecologic and pathologic laboratories of the Johns Hopkins Hospital—a period in which 402 cases of tuberculous salpingitis and 516 of tubal pregnancies had been observed.

In 1940, apparently as a result of a more thorough search of the literature, Bland² assembled 32 cases and added one of his own. This represented the only such case which had been observed in the Jefferson Medical College between 1907 and 1939, during which period some 55,000 surgical specimens had been examined. Of these, 209 represented tubal pregnancies and 38, tuberculous salpingitis. Since 1940, some four additional cases have been reported in the American and in the continental literature.

Our patient, S. G., aged 27, was first admitted to the Mount Sinai Hospital six years ago—3/27/36, with a three months' history of painful, bloody urination. Some weight loss had occurred. Physical examination disclosed a patient in apparent good health with no important findings, except a soft systolic murmur at the apex. There was no history of tuberculosis in the family or any past history of tuberculosis. An examination of the chest disclosed no clinical evidences of active tuberculosis. X-ray of the chest was normal. Urine from the right kidney showed acid-fast organisms, that from the left showed none. An occasional acid-fast rod was found in the feces. An intravenous urography done prior to operation disclosed a moderately enlarged right kidney, whose lower pole showed soft masses and a small amount of mineral deposits, as is occasionally seen in tuberculosis. The sputum at no time showed tubercle bacilli. A right nephrectomy was done. Histologic examination disclosed a tuberculous pyelonephritis with abscess formation. The patient was discharged after a month's stay, in apparent good health.

The patient was readmitted on 4/6/41, five years later, with a history of lower abdominal pain localized in the right abdomen which had persisted for the previous two days. In addition, during this period, vaginal bleeding had started. Her last menstrual period was 2/24/41. The patient had married since her discharge from the hospital. Urine analysis on this occasion showed 1 to 2 W.B.C. per h.p.f. and no R.B.C. The hemoglobin and red blood cell count were normal. A diagnosis of tubal pregnancy was made and on the following day, under spinal anesthesia, a right salpingectomy and appendectomy were performed. At operation, free blood was found in the peritoneal cavity and bleeding was noted from the fimbriated end of the right tube.

This tube was larger than normal and appeared indurated in its mid-portion. X-ray of the chest, done one week postoperatively, was entirely negative.

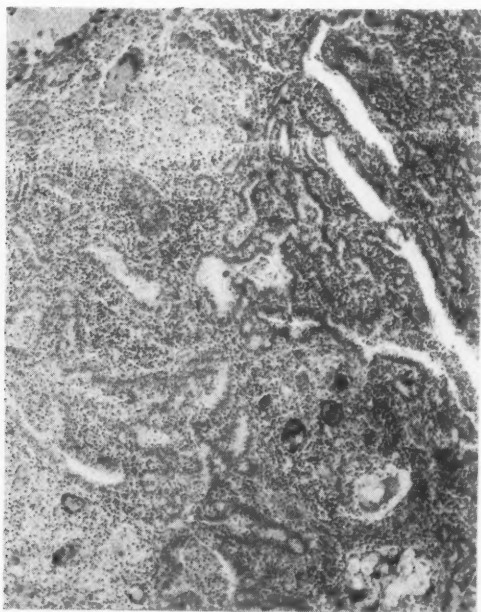


Fig. 1.—Section of Fallopian tube showing matted villi and tuberculous process. Note giant cells and tubercles. ($\times 100$.)

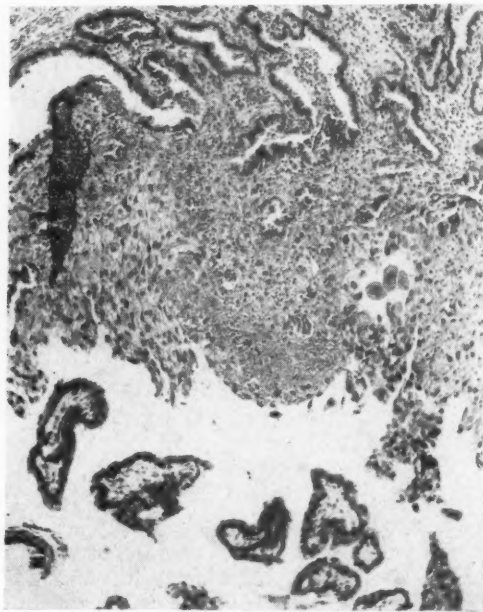


Fig. 2.—Section of Fallopian tube showing decidua and chorionic villi. ($\times 100$.)

Pathologic Findings.—The specimen consisted of a Fallopian tube measuring 6 by 1.3 cm. At its fimbriated extremity, a small amount of firm, dark-brownish blood was present. Its serosal surface was reddish-purple and smooth. Its wall was greatly thickened, considerably narrowing the lumen. The lumen at the uterine end contained thin, red blood. The fimbria were large. Microscopically, two processes were present—a productive tuberculous salpingitis (Fig. 1) and areas containing chorionic villi and decidual tissue (Fig. 2). Endometrial tissue passed three days following operation consisted of hemorrhagic, moderately inflamed decidua showing no evidences of tuberculosis. (Fig. 3.)

Her postoperative course was good. About 15 days after admission, she showed signs of a psychosis and insisted upon being discharged.

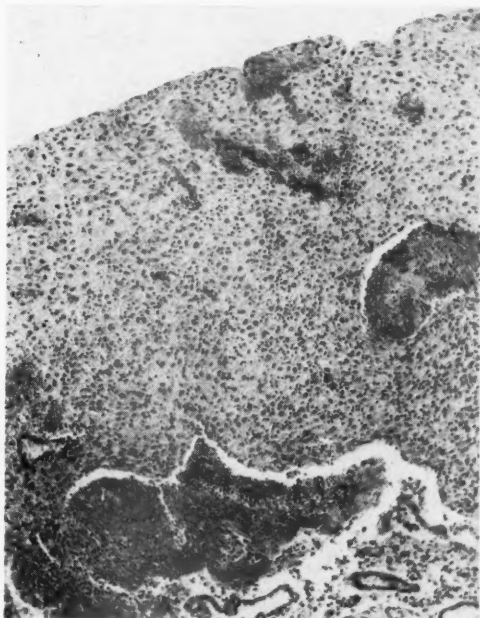


Fig. 3.—Endometrial tissue showing decidual reaction and absence of tuberculosis. ($\times 100$.)

Discussion

It is believed that the rarity of the association of tubal tuberculosis and pregnancy is probably in some measure due to the blocking of the lumina of the tubes to the spermatozoa and ova by the tuberculous process. Even should this obstacle be circumvented, it would appear that the nidation in the uterus is usually unsuccessful since in the series of 402 cases of tuberculous salpingitis studied by Stevenson and Wharton,¹ there was an 85 per cent incidence of associated tuberculous endometritis. Hence, the well-known association of sterility with tuberculosis of the genital tract. While there have been reported instances of conception in cases of tuberculous endometritis, probably as the result of the clearing of the process by successive curettements, there does not appear to be present the same opportunities for the clearing of the tubal tuberculosis. However, it should be noted that the lumen of the tube in tuberculous salpingitis may remain open to a slight

degree in the early stages of the disease and even in advanced cases. Since histologically the tuberculous process is often focal, there exists the setting for the rare occasion when the fertilized ovum may nidate and mature in an uninvolved or only slightly involved area. However, even should such a nidation be successful, because of the scarring brought about by the tuberculous process with the consequent diminished tubal elasticity, rupture usually supervenes before the fetus attains an appreciable size.

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2019 PINE STREET

Tietze, Christopher: Differential Reproduction in the United States—Paternity Rates for Occupational Classes Among the Urban White Population, *Am. J. Sociology* 49: 242, 1943.

This study is based on a portion of the National Health Survey of 1935 to 1936. To study and report the relationship between paternity and occupation is the purpose of the author. Occupational groups are divided into the professional, business, skilled and semiskilled, unskilled, and miscellaneous which includes farmers, farm laborers, etc. The highest paternity rate was in the skilled and semiskilled group, business group was next; unskilled, professional and miscellaneous followed in that order. The net paternity rate for the four classes was professional 0.68, business 0.69, skilled and semiskilled 0.86, unskilled 0.89. When these groups were studied on the basis of education it was found that the highest net paternity rate occurred in men who had seventh grade education or less (0.97), eight grade (0.86), High School (0.68), and college (0.52). On the basis of income the reproductive rates were: \$3,000 and over 0.42; \$2,000 to \$3,000, 0.61; \$1,500 to \$2,000, 0.70; \$1,000 to \$1,500, 0.86; under \$1,000, 1.17.

Considerable attention is given to classifying and breaking down the paternity rate into 3 subgroups and also in contrasting paternity rate with reproduction rate and correlating the two. These involve technical factors which should be of very material value to the sociologist or statistician but for the average physician it is rather difficult to analyze.

WILLIAM BICKERS.

SUCCESSFUL BRONCHOSCOPY FOR ATELECTASIS IN A SIX-HOUR-OLD INFANT

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BRONCHOSCOPIC examination in newborn infants is a recognized procedure but the use of the bronchoscope immediately after birth for the treatment of atelectasis is apparently rare. The following case is reported for two reasons: (1) the fact that the infant was but six hours old at the time of examination, and (2) to emphasize the value of immediate bronchoscopy in cases of atelectasis in newborn infants.

Delivery of the baby by one of us (D. D. D.) was by Porro-cesarean section because of a ruptured uterus. The throat was immediately aspirated with the tracheal catheter and the infant cried and seemed normal. Shortly thereafter, however, intermittent cyanosis developed. Examination showed marked retraction of the right chest with absence of breath sounds and dullness to percussion. The heart findings were normal. There were no signs to suggest cerebral hemorrhage but vitamin K was given. A diagnosis of atelectasis of the right lung was made. Treatment with carbon dioxide and oxygen inhalations was of no avail, nor did lying on the unaffected side relieve the condition.

The infant was well developed in every way and showed no abnormalities other than the atelectasis. It was felt that if the atelectasis was due to a blocking of the bronchus by mucus, bronchoscopy might be of help. Accordingly, a bronchoscope for newborn infants was passed by one of us (H. E. B.). The infant was then six hours old. A considerable quantity of thick, yellow secretion was aspirated from the trachea and a small amount from the right bronchus. The right bronchus seemed to be collapsed; there was a little chink at the carina and below this the membranes were quite red. Immediately following aspiration, aeration of the right lung was audible through the stethoscope, the right chest expanded to equal the expansion of the left side, and the breathing became normal on both sides. The baby's condition remained good for the duration of its hospital stay and when discharged, the baby seemed to be entirely normal.

Two months later an x-ray film of the chest, taken because of the development of a bronchopneumonia from which the baby made a rapid recovery, showed apparently complete expansion of the lung. The roentgenologic report stated "there is bronchopneumonia throughout the right lung which is completely expanded."

At the age of three and one-half months a fatal influenzal meningitis and bilateral otitis media developed. Autopsy was performed at the Children's Hospital in Buffalo by Dr. K. Terplan who found at that time, diffuse edema and slight atelectasis of both lungs, hyperplasia of the thymus and lymph glands, and moderate enlargement of the spleen.

The final unhappy outcome in this case does not alter the fact that the prompt use of the bronchoscope a few hours after birth undoubtedly saved the infant's life at that time. The extent to which any possible residual atelectasis may have contributed to the illnesses which followed, we do not know. We are reporting the case in the hope that it will stimulate interest in the use of the bronchoscope as a lifesaving measure in cases of atelectasis in newborn infants.

Department of Statistics

RUPTURE OF THE UTERUS

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THE reported incidence of rupture of the uterus varies considerably. Stander¹ reports 12 cases in a series of 27,125 consecutive deliveries, or one in every 2,260 labors at New York Lying-in Hospital. In a review of 51,571 cases from the combined services of the University of Maryland and the Baltimore City Hospitals, Reese and Linn² found this accident to occur once in every 1,516 confinements. However, the highest incidence of rupture of the uterus which the authors have been able to find is that reported by Whitacre and Fang³ from Peiping Union Medical College: among 11,500 obstetric admissions, there was one rupture in every 220 cases. Irving⁴ states that rupture of the uterus has been treated once in every 1,959 deliveries at Boston Lying-in Hospital.

Herewith is reported a series of 23 cases of rupture of the uterus, occurring in the 16-year period from 1925 to 1941. This group of patients includes all cases of this accident seen at University Hospitals of Cleveland (Maternity Hospital) during this period of time. In this 16-year period 34,295 deliveries were conducted at Maternity Hospital, and 29,096 patients were confined at home by the Maternity outpatient service of Western Reserve University, thus giving a grand total of 63,391 obstetric cases. Rupture of the uterus, therefore, has been treated once in every 2,756 deliveries seen on this obstetric service.

Age.—The ages of the patients varied from 19 to 38 years; the mean age was 28.4 years. Five of the 23 patients were 36 years of age or older.

Parity.—In the entire group there were only three primiparas, the average parity being 3.6. It is well known that multiparas experience this accident much more frequently than do primiparas. Schumann⁵ states the ratio to be 12:1; the ratio in our series, however, was 6.6:1.

Etiology.—The causative factors of rupture may best be considered by dividing the cases into the following five groups:

1. *Previous Cesarean Section.*—Rupture of a remote cesarean scar was the causative factor in 13, or 56 per cent of the 23 cases. All of the previous sections were of the classical type; no case of rupture following laparotrachelotomy was encountered in this series. Six of the patients had had 2 or more cesarean sections, whereas 7 patients had had but one previous section. The mean number of previous sections was 1.5. One patient had had 3 previous sections.

TABLE I. ETIOLOGIC FACTOR ASSOCIATED WITH 23 CASES OF RUPTURE OF THE UTERUS

ETIOLOGIC FACTOR	NO. CASES	PER CENT
Cesarean scar (classical)	13	56 plus
Podalic version	6	26
Oxytocic agent	1	4
External trauma	1	4
Undetermined (spontaneous intrapartum)	2	8

All of the ruptures occurring in the previous section group were spontaneous in onset. Five, or 38 per cent of the 13 cases occurred before the onset of labor, but all were at or near term, excepting one which happened in the eighth month of gestation. The other cases (68 per cent) occurred after the onset of labor, which varied from one to twelve hours, and all of these individuals were at or near term.

In fairness to the classical operation, it should be stated that the dictum "once a cesarean, always a cesarean" had not been followed at this clinic until approximately ten years ago, since which time laparotrachelotomy, rather than the classical operation, has been the most frequently performed type of abdominal delivery. Prior to the last decade, any number of patients were allowed vaginal delivery after previous section, provided, of course, the indication for section had been a temporary one, such as placenta previa, or toxemia of pregnancy. Whenever pelvic contraction had been the indication for the original section, naturally enough all subsequent pregnancies were terminated by elective section. It has been in the last decade only that the policy of doing elective section on all previous cesarean patients has been followed in all cases, regardless of the nature of the indication for the original abdominal delivery. These facts are related so that conclusions drawn from a comparison of the classical versus the low cervical operation will not be misleading.

2. *Internal Podalic Version.*—This procedure accounted for 6, or 26 per cent of all the cases of uterine rupture. The indication for version was persistent vertex occipitoposterior position in 5 of the cases, and compound presentation (arm and leg) in the sixth case. Version was carried out successfully in 3 of the 6 cases, but failed in 2 others, in one of which a contraction ring was recognized. In one case included in this category, version itself was not actually attempted, inasmuch as the uterus was found to give way when the operator introduced his hand into the uterine cavity.

3. *Oxytocics.*—The administration of an oxytocic agent (crude ergot) accounted for one case, or 4 per cent of the total series. That was a para iv, aged 37 years, who had been given a hypodermic injection of ergot by a midwife to stimulate labor pains. The patient was admitted later to Maternity Hospital for treatment. Laparotomy revealed a complete rupture at the level of the internal os, which had dissected the peritoneum from cecum to sigmoid. There was remarkably little bleeding, and minimal shock. Curiously enough, none of the major vascular supply to the uterus had been implicated by the rupture. Supracervical hysterectomy and salpingectomy were followed by complete recovery.

Inasmuch as pituitary extract is practically never used on this obstetric service until the third stage of labor, it is understandable how no case of rupture due to this agent is reported in this series of cases.

4. *External Trauma.*—A fall on the abdomen was the precipitating factor in one patient, or 4 per cent of the series: This was a 30-year-old-

primigravida, who was admitted to Maternity Hospital in her seventh month of pregnancy, because of hydramnios accompanying twin pregnancy. The patient was put to bed and given barbiturates to relieve the discomfort due to distention. While under the effects of barbiturates, the patient got up out of bed and fell prostrate on the floor, where she was found in shock. Laparotomy revealed both twins free in the abdomen; one of the fetuses was stillborn, whereas the other died shortly after delivery. Supracervical hysterectomy was performed, and the patient recovered after a convalescence complicated by intestinal obstruction and pelvic cellulitis.

Doubtless, the twin pregnancy with its accompanying hydramnios was an etiologic factor in the case just cited. In retrospect, it probably would have been better to have relieved the hydramnios by artificial rupture of the membranes.

5. *Undetermined Etiology.*—Two cases of spontaneous intrapartum rupture of undetermined etiology were seen. The first patient in this group was a 22-year-old para iii who died almost immediately after the spontaneous delivery of a 7-month stillborn. Autopsy revealed a complete rupture; unfortunately, nothing is known about the previous obstetric and gynecologic history of this patient. The second patient, a 34-year-old para iv, had an easy labor, and low forceps delivery, but suddenly went into profound shock, and expired during laparotomy, despite 2,350 c.c. of whole blood, and 500 c.c. of serum. Operation revealed an incomplete tear in the lower uterine segment, 6 cm. in length, and located below the bladder-flap. The cause of the rupture in this case, too, is shrouded in mystery. The authors are inclined to the belief that perhaps an old cervical laceration might have given way during labor, with extension of tear into the lower uterine segment, as suggested by Gordon and Rosenthal.⁶ No other explanation as to why these two uteri ruptured spontaneously seems likely. Both patients were multiparas; both had easy labors; and both had uncomplicated deliveries. One can only surmise that the cervix was at fault.

Degree of Rupture.—Of the 23 cases, 17, or 74 per cent were complete ruptures, that is, extended through the peritoneal covering of the uterus; on the other hand, 6, or 26 per cent were partial ruptures, consisting of subperitoneal extension of the laceration, with hematoma-formation between the leaves of the broad ligament. All but 2 of the cases resulting from previous cesarean section were of the complete variety. Half of the version cases were complete; half were partial.

TABLE II. FREQUENCY OF COMPLETE VERSUS PARTIAL RUPTURE

GROUP	COMPLETE		PARTIAL	
	NO. CASES	PER CENT	NO. CASES	PER CENT
Cesarean scar	11	85	2	15
Version	3	50	3	50
Oxytocic	1	100	0	0
External trauma	1	100	0	0
Undetermined	1	50	1	50

The diagnosis of rupture of the uterus was made in one near-term secundipara who complained of lower abdominal discomfort for 60 hours; examination showed a bulging fluctuant mass, 2½ cm. in diameter, presenting under the lower midline scar. This patient experienced a stormy convalescence after her first cesarean section. The

preoperative diagnosis of membranes herniating through a defect in the anterior uterine wall was confirmed at laparotomy.

A Bandl contraction ring was diagnosed in 2 patients who proved later to have ruptured uteri. In both instances, internal podalic version was attempted in the face of a contraction ring, an absolute contraindication for podalic version. In 2 other cases undue resistance was encountered in executing the version, due to inadequate uterine relaxation, a *sine qua non* for successful version. In the fifth rupture due to version, the uterus, which previously had seemed adequately relaxed, "clamped down" during version, with resulting rupture. In the sixth case, as the operator's hand was introduced to perform version, a rent in the lower uterine segment was recognized. The indication for podalic version in 5 of the 6 cases was high persistent vertex occipitoposterior position; in the other case the indication was compound presentation.

Treatment

Operative treatment was carried out in 22 of the 23 patients. The only one who received no surgical treatment was a patient who had sustained a spontaneous intrapartum rupture of undetermined etiology; death ensued before blood transfusion, etc., could be arranged. Supracervical hysterectomy (7 times) and Porro cesarean section (6) were the most commonly performed surgical procedures. Simple repair of laceration was done three times. Each of the other operative procedures, vide *infra*, was done once each.

TABLE III. OPERATIVE PROCEDURES PERFORMED UPON 22 PATIENTS

OPERATION	NO. CASES	DEGREE RUPTURED	
		COMPLETE	PARTIAL
Supracervical hysterectomy	7	6	1
Porro section	6	4	2
Repair laceration	3	3	0
Supracervical hysterectomy and salpingectomy	1	1	0
Supracervical hysterectomy and salpingo-oophorectomy	1	0	1
Panhysterectomy	1	0	1
Classical cesarean and tubal ligation	1	1	0
Laparotrachelotomy	1	0	1
Laparotomy	1	1	0

Maternal Mortality

Of the 22 patients operated upon three sustained immediate operative deaths, i.e., expired during operation; one succumbed to peritonitis

TABLE IV. TABULATION OF MATERNAL MORTALITY

OUTCOME	NO. CASES	PER CENT
Immediate intrapartum death	1	4 plus
Expired during or immediately after operation	3	13
Succumbed to peritonitis	1	4 plus
Recovered	18	78
Total	23	100

on the fifth postoperative day. In all, 18 patients survived, thus giving a gross mortality of 22 per cent, consisting of an immediate surgical mortality of 13 per cent, and a postoperative mortality of 9 per cent.

Analysis of Fatal Cases

CASE #16-222.—Para ii, aged 20 years. One previous cesarean section for contracted pelvis and disproportion. In active labor with floating head for 8 hours, before section was started. Just prior to operation patient went into shock, and expired during laparotomy. Free blood in peritoneal cavity. Saline infusion was the only supportive treatment given (1926).

Comment: Had operation not been so long delayed after the onset of labor, rupture probably would not have occurred. Moreover, whole blood and/or plasma would have improved tremendously the chances of survival after the onset of shock.

CASE #19-043.—Para vi, aged 28 years. Two previous cesarean sections for mitral stenosis. History of constant pain in left lower abdomen for 18 hours before section was started. Much free blood was encountered as soon as abdomen was opened, whereupon the patient went into immediate and profound shock, expiring 20 minutes after incision had been made. No antishock treatment at all (1927).

Comment: Earlier operation, and modern antishock therapy, as practiced today, would probably have reversed the outcome.

CASE #27-346.—Para vii, aged 37 years. Rupture occurred during attempted version for high persistent vertex occipitoposterior position, despite the presence of a contraction ring (1931). Death occurred on the fifth postoperative day from peritonitis and paralytic ileus. Hysterectomy had been done for complete rupture.

Comment: The local use of sulfonamides, as practiced today, plus parenteral sulfonamides, and Miller-Abbott tube following operation would be in order in the management of such a case today.

CASE #39-534.—Para iii, aged 22 years. Rapid labor with severe pains, followed by the spontaneous delivery of a 7-month stillborn fetus. Profuse and fatal postpartum hemorrhage, although fundus contracted firmly at regular intervals. Intravenous saline and acacia solution (400 c.c.) were the only supportive treatment given (1936). Patient expired before transfusion could be arranged. Nothing is known about the previous obstetric and/or gynecologic history.

Comment: The etiology is obscure. The most likely cause seems to be the possibility of the giving way of an old cervical laceration, with extension of tear into the broad ligament. Three such cases have been reported by Gordon and Rosenthal.⁵ The precipitous character of the labor should have been slowed down by the timely use of analgesics and anesthetic agents. It is readily understandable how an old cervical laceration, especially one which had escaped notice, or for other reasons had not been properly repaired at the time of a previous delivery, could have given way during a subsequent labor, particularly during one characterized by rapid dilatation of the cervix. Extension of such lacerations, as suggested by Gordon and Rosenthal,⁶ may explain the spontaneous rupture occurring in the apparently normal uterus of the "*grande multipara*."

CASE #53-283.—Para iv, aged 34 years. Easy labor (16 hours); low forceps delivery, followed by profuse and persistent postpartum hemorrhage, which continued unabated despite packing and intravenous ergotrate. Notwithstanding 2,850 c.c. of whole blood and serum, this patient expired during operation, which disclosed a partial rupture of the lower uterine segment (1941).

Comment: Unfortunately nothing is known of the past obstetric history of this patient. The only tenable explanation of rupture would seem to be the possibility of the giving way of a scarred cervix, with extension of laceration into the lower uterine segment.

Fetal Salvage

Of the 24* fetuses 14 were stillborn; 9 survived, and there was one neonatal death.

TABLE V. TABULATION OF FETAL SALVAGE

OUTCOME FOR FETUS	NO. CASES	PER CENT
Stillborn	14	58
Survived	9	38
Neonatal death	1	4
Total	24	100

Summary

1. A series of 23 cases of uterine rupture has been reviewed. The etiology, clinical picture, treatment, and prophylaxis of this obstetrical catastrophe have been discussed.

2. All patients who experienced rupture of the uterus following cesarean section had had the classical operation; no instance of rupture subsequent to laparotrachelotomy was encountered in this series.

3. Six cases of rupture were attributed to internal podalic version and breech extraction. The conditions essential for safe and successful version have been stressed.

4. The possibility of old cervical lacerations giving away during labor has been suggested as a not unlikely explanation for certain cases of rupture in multiparas, in the absence of more overt causative factors.

5. Of the 23 mothers, 18 survived. However, with the more modern methods of treatment available today, probably 4 of the 5 fatal cases would not have succumbed.

6. The fetal salvage was 38 per cent.

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*From the group of 23 mothers there were 24 fetuses, due to the fact that one mother had twins.

Special Article

CONTRAINDICATIONS AND CAUTIONS IN THE USE OF CONTINUOUS CAUDAL ANALGESIA*

ROBERT A. HINGSON, M.D., SURGEON, U.S.P.H.S., PHILADELPHIA, PA.

*(From the Philadelphia Lying-in and the Women's Department of the
Pennsylvania Hospital)*

CONTINUOUS caudal analgesia is a natural outgrowth from a combination of the principles of several procedures practiced in anesthesia during the last four decades. Sicard and Cathelin of France in 1901, first used the sacral hiatus as the approach to the extradural space for their injections of cocaine solutions in order to block the nerves transmitting pelvic pain in the specialty of urology.

Stoeckel (1909), and later Schlimpert (1911) of Germany, first applied this method for the relief of pain in obstetrics. They utilized the drug novocain which had recently been prepared by the chemist Einhorn to replace the more toxic cocaine. Their method completely relieved the pains of delivery for a period of thirty minutes to one hour in suitable cases.

In 1921, Pagés of Spain made use of the extradural space for nerve block in surgery through the interspinous lumbar approach. Dogliotti of Italy further refined this technique and demonstrated its use as the method of anesthesia for surgery of the lower two-thirds of the body.

In America Meeker, Bonar, Campbell, Rucker, Thompson, Labat, Lundy, Sword, Baptisti, Odum, Lahman, and Mietus made valuable contributions to the art of single-injection caudal analgesia and anesthesia in the various branches of medicine, surgery, and obstetrics. Grafanino dramatically achieved the same results in obstetrics by using the approach of Pagés and Dogliotti.

All these men recognized the advantages and hazards of the single injection to achieve an effective nerve block for a very limited space of time depending upon the pharmacologic effect of the drug used. They all stressed the contraindications and complications of their experience in warning physicians to safeguard the patient against the hazards attendant upon its use and misuse.

Recently (in 1941) the author, in collaboration with Edwards and Southworth, cognizant of the advantages of Lemmon's new refinement of continuous spinal anesthesia, introduced continuous caudal analgesia for both surgery and obstetrics. Almost immediately both medical and nonmedical writers of the lay press seized upon the scientific reports

*Published with permission of the Surgeon General, U. S. Public Health Service.

to the profession of this work with such an acclaim and "blast of trumpets" that both the lay public and the bystanding physician have become the victims of distortions, misrepresentations, and literary salesmanship. The result has been a dangerous demand on the part of the obstetric patient for a method of pain relief that is still in the developmental stage and a reactionary defense on the part of the physician who has been forced to deflate the enthusiast with the sharp edge of conservative caution.

The fact remains that more than one hundred lay articles have appeared in the press from the pens of authors who have never once seen continuous caudal analgesia nor are they familiar with obstetrics. As a result, thousands of women are led to believe that continuous caudal analgesia can be purchased across the counter in every maternity section of all hospitals as a panacea and a happy detour from the usual experiences of childbirth.

On the developmental side of the problem, one hundred and sixty clinics have already reported more than 30,000 births managed with this technique. This method has been used in more than half the countries of the world. Apparently, many more thousand attempts have been made with some mixed results in instituting the technique. The promised "dramatic relief of all pain" attendant upon the act of childbirth has not been fulfilled in all cases in both unskilled and skilled hands.

I believe that continuous caudal analgesia, when properly administered, will completely relieve the pains of labor and delivery. The pain relief of this procedure receives a disproportionate emphasis when reviewed against the background of the vigor of the first cry of the newborn infant, uninfluenced by narcotization and anesthesia, the diminished third-stage blood loss, and the rapidity of post-partum convalescence.

Nevertheless, the limitations of the technique should be evaluated; it is not a procedure to be used in the home and in the poorly staffed hospital. This eliminates more than 70 per cent of American births from consideration. In addition, we estimate that 40 per cent of parturients delivered in well-staffed maternity units present contraindications prohibiting its successful use in the early experience of any clinic. Thus, if every hospital in the United States utilized this form of obstetric management in every suitable case, only 12 per cent of women could benefit from this form of pain relief. The truth remains that not more than one hospital in ten is utilizing this technique at all. In all probability this means that less than one per cent of American mothers will have this method for the next five years. This is a far distant objective from the "almost universal use of the method" promised to American women by the uncensored lay publicity.

In our experience we believe the contraindications to the method are the following:

1. Patients with easy, almost precipitate labors and patients who come into the hospital in the terminal part of the second stage of labor, less than forty minutes before delivery—for them a few whiffs of gas or ether, and, in the selected short cases, even chloroform, are safer and more satisfactory than caudal analgesia. This group includes an estimated 10 per cent of hospital deliveries.
2. Patients who are apprehensive, nervous, and desirous of being asleep when the baby is born and those who profess a fear of caudal analgesia because of the needle injection or because it is to them an "experimental" procedure, do not as a rule make good patients under this technique and should be excluded. They represent about 10 per cent of hospital obstetric patients.
3. Gross deformities or disease of the spine or central nervous system, including syphilis of the central nervous system, tumors which narrow the spinal canal, abnormal extension of the sacral hiatus, abnormally low extension of the dural sac, history of epilepsy, hysteria, and emotionally unstable personalities preclude the use of this method. Trotter, on the basis of a study of several thousand sacra, estimated that more than 5 per cent have anatomic deformities in and around the sacral hiatus which would exclude successful use of the method. This group excludes another 10 per cent.
4. Extremely obese individuals with large fat pads over the sacral hiatus preventing accurate palpation of the hiatus and adequate insertion of the caudal needle should not receive caudal analgesia. Approximately 3 per cent of patients can be listed in this group.
5. Local infection (bacterial or fungus) at the site of the injection and patients with real, removed, and potential pilonidal cysts contribute to another 2 per cent of the contraindications.
6. Profound anemia and dehydration, unless supplemented by oxygen inhalations and intravenous fluids.
7. The obstetric complications can be grouped under one section:
 - a. Placenta previa unless used for immediate cesarean section.
 - b. Abruptio and incomplete or beginning premature separation of the placenta.
 - c. Patients with definite disproportions of pelvic and fetal diameters unless used for a trial of labor preliminary to a cesarean section.
 - d. Nulliparous patients with a floating and unengaged fetal head and patients with pendulous and weak abdominal walls in the presence of an unengaged fetal head.
 - e. In the birth of monstrous and predetermined dead babies.Approximately 5 per cent of hospital deliveries fall into this group.

8. History of sensitivity to the analgesic agent is an extremely rare but, indeed, definite contraindication.

Thus, we advise that these contraindications be observed rigidly by those beginning the use of caudal and continuous caudal analgesia.

The incidence of the successful use of this method can be increased if the hospitals and clinics anticipating its application would adopt a form of organization and teamwork between the obstetric and anesthetic staffs with an adequately trained nursing supplement.

First, the physicians using the technique should have a period of special training involving a study and correlation of anatomy, physiology, pharmacology, and the altered obstetrics produced with this method.

Second, the patient should be surrounded with safeguards of readily available oxygen, vasopressors, and sterile lumbar puncture needles for withdrawing the occasional inadvertent massive spinal injection that might result from carelessness for indicated cases.

Third, diligent attention should be given the supplementary diagnostic aids of the Bishop x-ray technique for minute study of the sacrum to rule out insurmountable anomalies. The results of the tocographic tracings now being performed in several hospitals should be watched for a study of uterine motility under caudal analgesia.

It should be emphasized that continuous caudal analgesia should not be continued indiscriminately. More than 80 per cent of the last one thousand cases managed in the Philadelphia Lying-in Hospital were given this form of pain relief for less than five hours per patient. It was designed to relieve the pains, not the early discomforts of labor. The incidence of failures and refractory pain rises sharply after eight hours of caudal analgesia.

The reported complications thus far encountered in 30,000 cases include 12 maternal deaths. Seven of these probably could have been avoided if the above criteria had been carried out. Three were definitely anesthetic deaths that related to a misuse of the principles and substituted principles. The small incidence of infection, the associated minor complications of drug reactions, postanalgesic aches and pains, and the incidence of failures approaching 10 to 20 per cent in even expert hands have been previously reported but should serve to emphasize that the method is not infallible and should be considered still in the developmental stage.

The originators of the method are still studying the many new problems associated with the technique and solicit the consultation of specialists in obstetrics and anesthesia in protecting the patient from the enthusiasts, the untrained, and the propagandist. With the obstetric collaboration of Doctors Vaux, Lull and the staff of the Philadelphia Lying-in Hospital, the labors and deliveries of more than 3,000 patients have been managed with this technique. We are convinced the method opens up a new horizon to the medical profession.

Editorial

Again, Caudal Anesthesia

THE April, 1943, issue of this JOURNAL included an editorial on the subject of caudal anesthesia in obstetrics, in which attention was called to the rapidly spreading employment of this procedure, fathered as it was by extensive publicity both in lay and certain medical periodicals, and to the need of caution in its application. Contributions in great number have been added to the literature on the subject and thousands of cases reported with apparently favorable immediate results. Uniform standards of technique, however, have not been generally adopted and various authors have developed their own particular variations as to the choice of the anesthetic agent and the method of approach. In view of the general interest in the subject, we opened the pages of this JOURNAL for the publication of reliable and informative articles dealing with caudal anesthesia but found it necessary to exercise restraint in their acceptance unless they constituted definite additions to our knowledge of this procedure. What is still needed is the presentation of frank confessions of failures and complications. In no other way can a sound evaluation be made.

What may be regarded as a relief to the somewhat unrestrained endorsement of a captivating and dramatic procedure, is the admission by those who have had an extended experience and given careful thought to the matter, that this is not a measure for the relief of labor pains entirely free from risk, that it must be carried out by a specially trained personnel, that it is only to be employed in an adequately staffed and supervised hospital service with adequate cooperation between the anesthetist and the obstetrician. In other words, it is not to be accepted as a routine procedure nor as a salvation for mere pain relief. There are numerous "don'ts" to be observed, as shown in the recent article by Clifford Lull,* and the "Stop, Look and Listen" sign displayed at unattended railway crossings still may be regarded as an effective if rather blunt danger signal by way of comparison.

Attention therefore is directed to the special article which appears on another page by Dr. Hingson, a proponent of the method and experienced in its use. We present it as a warning note in view of possible unfortunate developments if caution is disregarded in employing in what may prove in selected cases, a valuable addition to our obstetric armamentarium.

*Lull, C. B.: AM. J. OBST. & GYNEC. 47: 312, 1944.

Measures to alleviate the "pains" of labor have come and gone. One after another they were hailed as the *sine qua non* of proper delivery care but the continued search for new methods must be accepted as evidence that ultimate success is still to be achieved. It would be unwise and unjust to decry the efforts of those who desire to provide relief, when required, to women in labor but it seems equally unwise and unjust to prospective mothers to make them believe that each new procedure is generally applicable, or that it is absolutely safe for themselves or their babies. Thus there is still need for a more definite evaluation of caudal anesthesia, which cannot be regarded otherwise than as a major surgical procedure of equal importance with the obstetric conduct of the labor itself. The "don'ts" which must be taken into account by those who are tempted to resort to this method, and which have been stated so frankly by competent observers should receive commensurate publicity with the widely heralded advantages. We have by no means reached the goal.

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Correspondence

Artificial Insemination

To the Editor:

It is commonly accepted in medicine that chronological precedence on this earth gives no one and no group any priorities flowing from a celestial O.P.A. or other heavenly agency. Medicine cannot recognize vested interests or rights even if it must, along with the rest of the community, appreciate terrestrial wealth and power. Scientific facts must be recognized from whatever source they come. We cannot degenerate to Nazi levels of thinking that anything we originate has a halo about it whereas anything that comes from the other fellow (not in our group or crowd) is false; is to be ignored and despised.

In 1941, we analyzed¹ the replies of several thousand physicians to the questionnaires sent by the **National Research Foundation for the Eugenic Alleviation of Sterility, Inc.**, of Nesconset, L. I. Two years later a criticism of that analysis appeared.² We reviewed our material, including the printed article, the reprints thereof and the mimeographed sheets covering the findings which were distributed among physicians generally. We conclude without hesitation that we need offer no apology for what was written there except for the acts of our staff who failed to discover an erroneous statement of the totals of direct viable pregnancies. This should have been 3,523 boys (instead of 3,623) and 2,205 girls (instead of 2,105). However, the totals of these direct viable pregnancies, 5,728, and the grand total of all viable pregnancies, 9,238, were absolutely correct. We are glad to acknowledge further that an omission of 12 stillbirths was made although it was clearly stated in paragraph 2, of page 2 of the reprint that the number of surgical operations prevented (382) was 32 times as great as the number of stillbirths. A simple calculation would give the answer. We also wish to report that the mimeographed sheets mentioned that there were three sets of twins in the series. Through an oversight this was not included in the paper as it appeared in the *Journal of the A. M. A.*¹ We stated that 97 per cent of pregnancies gave living babies. By that statement we meant that the total of all viable pregnancies constituted 97 per cent of the grand total of all pregnancies; and so it was.

If any of these figures seemed too great or too small to the expert calculators who live in the realm of the slide rule, we have no explanation or apology to offer because the questionnaires reflected not the work of the authors but of the more than 7,000 doctors who replied.

Criticism was made on page 918 of the June article in this JOURNAL which demonstrates the failure to appreciate the difference between "pregnancies" and "viable pregnancies." That this should not seem clear to the physicist who was mysteriously drawn into the question as an expert is not surprising, but that a physician such as the reviewer, who adopted the conclusions of the physicist should not understand the difference is more than astonishing. It needs hardly be pointed out in these pages that all of those who become pregnant and give birth to live issue are termed viable pregnancies. Every woman who became pregnant was counted as a case of pregnancy initiated. When she became pregnant the second time, she was counted as a second case just as is done in clinics and in private records throughout the land.

¹Artificial Insemination: Present Status in the United States as shown by a Recent Survey, Seymour and Koerner, J. A. M. A. 116: 2714, June 2, 1941.

²Status of Artificial Insemination, Clair E. Folsome, AM. J. OBST. & GYN. 45: 915, June, 1943.

Much was made of the insemination curve, and a tortured analysis led the reviewer to remark that there were less than 100 pregnancies in which 8 inseminations had been employed and that the next point on the graph showed 4,312 cases in which 12 inseminations were used. This was stated to demonstrate that there was 43 times as great a chance to become pregnant with 12 inseminations as with 4 to 8. Yet the critic admitted there were no reports for 4, 5, 6 or 7 inseminations.

However, the actual number of successes from 8 inseminations was reported by us as 61. The number for 12 inseminations (4,312) is therefore about 70 times (not 43 as stated by the reviewer) that for 8. This number (4,312) is about 10 times as great as reported for 3 inseminations but less than five times that reported for 9 inseminations. The reviewer chose to ignore entirely that there were almost 900 cases (897 to be exact) for 9 inseminations and proceeded to the number for 12. Perhaps this was accidentally omitted; certainly to include it would not seem to fit into the argument of his review.

Now, what do all these figures indicate as to incidence of successful insemination? No more and no less than the bare fact that successes occurred and were reported at these levels; certainly not the tortured misinterpretations and omissions of our critic.

By now it must be evident that our critic's own accuracy is not above review. And so it is. We are by no means finished with the flow of inaccuracy that came from his pen. He stated² on page 922 that our report showed that 2 out of every 3 doctors obtained parallel success. This statement does not coincide with what we wrote. We reported 7,642 replies of which 4,049 were successful. This is roughly a little more than one-half, and not two out of three.

In his reading matter the reviewer cited an article on sperm by Rubenstein as reference 61 while his bibliography listed that number for an article by Langman and Burr. We were interested in this reference and looked it up only to find that it was listed on the wrong page. When we finally found the article, we discovered it had nothing whatsoever to do with sperm but treated the subject of ovulation and its electrometric timing. To test the accuracy of the sarcastic comment cited as references 65 and 66, we took the trouble to look at these volumes. We found that 65 was a general article on "The Perpetuation of Error in Obstetrics and Gynecology" and apparently was referred to solely for the purpose of quoting the phrase "perpetuation of error." We submit this is everyday English and requires no bibliography unless it is the reviewer's purpose to add the weight of a name in medicine to an argument about which that person never wrote and about which the reviewer himself is not too sure.

Number 66 was even more illuminating, as it referred to a publication by K. Hyder which was cited as "Human Affairs 2: 37, 1941." Search for this in the library of the New York Academy of Medicine was entirely unproductive. We then went to the central branch of the New York Public Library at 42 Street where they searched through the Union lists and all other lists of which they had knowledge to determine whether this was a discontinued publication. No trace of it ever having existed could be found. So that no charge of incompleteness be levelled against us, we then inquired at the general library of Columbia University. They had no record of ever having heard of it. We concluded with a search at the library of the College of Physicians and Surgeons of that University with the same result. We simply list these inaccuracies to indicate that errors arise in spite of painstaking checking in the hands of even those who set themselves up as supervisors over the work of others. Charity forbids that we multiply the example.

Finally, we cannot overlook the editorial in the same issue of this JOURNAL.³ The editorial writer stated that he wondered whether it is "desirable to lower the accepted human relationship in this respect (not in quote: substituting artificial

³Editorial: AM. J. OBST. & GYN. 45: 1066, June, 1943.

insemination for coitus) and in a sense to place them on a level with the propagation of animal life undertaken for convenience and gain." It is evident that such an opinion arises from a misconception of the facts. Artificial insemination is as much a modality for the treatment of sterility as the sulfa drugs are for infections. You would not think of refusing to employ the therapeutic marvels of the sulfa drugs just because we did not come supplied with them at birth? Shall we refuse to use insulin for the diabetic who needs it just because nature has failed to supply it in the patient's own tissues? Similarly, no one can refuse the last ray of hope remaining to the sterile—artificial insemination—in whom Nature has weakened or entirely cut off the ordinary source of his fertility.

The editorial further stated that the Christian and legal idea of marriage with its rites and responsibilities would likely be thrown into the discard through the employment of artificial insemination. On the contrary, neither of these systems of regulating human deportment are involved in artificial insemination as that is a method designed to perpetuate the marriage and allay the disrupting influences of infertility.

The commentator asked whether we can afford to overthrow the morality of the marriage state and approve the accompanying "unphysiologic" practices essential for this procedure (artificial insemination). The first part of this query has been answered above. A true appreciation of the procedure and the indications for artificial insemination will show the reader at once the error of the second argument.

In spite of all that has been learned about female physiology the secret of ovulation⁴ has escaped us so far. Our ability to raise depressed or absent spermatogenic function is extremely limited. The married woman who is capable of impregnation but has a sterile mate very often is subject to a procreative urge which is irrepressible. How can she become with child other than through artificial insemination? What other choice has a woman who is infertile? Would those who argue against this method prefer polygamy, prostitution or adultery? To permit sterility to continue would be unphysiologic and would constitute race suicide. What the practitioner seeks to do by artificial insemination is to enable the physiologic processes of pregnancy to take place and save a worthy couple from the desolation of enforced barrenness or the disrupting influences of divorce.

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ALFRED KOERNER, M.D.

Reply by Dr. Folsome

To the Editor:

Facts are stubborn things while hopes and figures are their aversion. Witness the "scientific" rebuttal, nine months delayed, of our medical confrere, Dr. Koerner, in the current issue of this JOURNAL, to our critical review on, "The Status of Artificial Insemination."¹

It appears plain the principal proponents of that inquiring organization, *The National Research Foundation for the Eugenic Alleviation of Sterility, Inc.*, exhibiting one projected function in its unwieldy title, now claim to question the facts in our critical review. Their refutation is welcome. We heartily urge the reader to review the two articles under consideration.^{1, 2} In our opinion, the analytic remarks require no subtraction but rather one addition. Several months prior to the release of this critical review¹ of the Seymour and Koerner survey article,² the writer, in the company of a well-known gynecologist, Dr. Robert L. Dickinson, made a personal call upon Dr. Seymour for the express privilege of discussing the artificial insemination survey. As workers in the same scientific field, we asked many questions about correlations derived from their survey. As humble students manifesting

⁴Editorial: Detecting the Exact Time of Ovulation by Ovulation Potentials, J. A. M. A. 124: 298, 1944.

scientific curiosity, we asked Dr. Seymour about her documentary evidence hoping, as do most visiting fellow scientists, we would have the customary accorded privilege of reviewing her voluminous original source data. As the interview became prolonged, we openly requested this usually granted privilege. Our earnest efforts met a firm refusal from Dr. Seymour. It is this fact more than any other which prompted the critical analysis of the paper in question. The original data upon which it was based not being made available, is it little wonder that our scientific credulity was strained. The evidence as listed in the article under consideration was cloaked with a scant degree of objectivity as to methods and in arriving at such bold conclusions that a critical review was all the more clearly indicated.

Dr. Seymour revealed no information in the original article of the method employed, whether by intracervical or merely vaginal instillations of semen. What were the criteria, as used by those answering Dr. Seymour's survey, in the selection of cases assigned to the group using heterologous semen specimens? What scientific reasons were given by the answering physicians for the use of donor semen? Where are the time correlations as related to the time of insemination? These observations would have tremendously enhanced the value of the survey.

Is it little wonder we sought the aid of a skilled mathematician among others, who gave liberally of their time, to assist us in a critical evaluation of the article² as it was presented? It was solely from this fragmentary evidence that the mathematical data concerning the survey per se were obtained. Our conclusions based upon the only available numbers, submitted in publication by Seymour and Koerner themselves, remain still unchanged. We request the indulgence of the reader and ask that he or she again reread our analysis.

The writer admits two bibliographical errors, one of omission anent Rubenstein, and one of commission regarding the crediting of the omitted Rubenstein reference (*Federation Proceedings* vol. 1: No. 1, March, 1942) to Langman and Burr, an article which should have been listed independently. The original copy contained even more references. These were subsequently omitted in order to condense the review. The writer is indebted to Dr. Koerner for having these errata directed to his attention. Incidentally, the editorial "Canned Knowledge" in *Human Affairs* 2: 37, 1941, can be obtained from the files of the National Committee on Maternal Health, in the building of the New York Academy of Medicine.

It is unfortunate that Dr. Koerner has apparently missed the total purposes of our critical review on "the Status of Artificial Insemination."¹ We cannot endorse promiscuous heterologous artificial insemination. Upon indication, after careful study of each individual case, homologous artificial insemination may be advisable.

In the words of Guttmacher³ which we emphatically reiterate, "*artificial insemination must never be an assembly line kind of medical treatment. . . .*"

In conclusion, the writer insists once again—"the principal reason for this critical review is to place on record a protest against publication of such extreme claims on the subject of human sterility until these are checked and verified." That conclusion stands for the reason stated by the writer in his original article¹ to which he invites the close scrutiny of interested readers.

A man protesting against incompatible fact is on the way toward uniting himself with all men that believe in truth. It is indeed a privilege to be in such complete accord with men like Guttmacher, Cary, Dickinson, Kosmak, et al. regarding heterologous artificial insemination.

CLAIR E. FOLSOME, M.D., F.A.C.S.

PLAINFIELD, N. J.,
MARCH 4, 1944.

¹Folsome, C. E.: *AM. J. OBST. & GYNEC.* 45: 915, June, 1943.

²Seymour, F. I. and Koerner, A.: *J. A. M. A.* 116: 2747, 1941.

³Guttmacher, A. F.: *J. A. M. A.* 120: 442, 1942.

Department of Reviews and Abstracts

Selected Abstracts

Placenta

Wang, H. W., and Hellman, L. M.: Studies in the Metabolism of the Human Placenta: I. Oxygen Consumption in Relation to Ageing, Bull. Johns Hopkins Hosp. 73: 31, 1943.

1. The oxygen consumption of human placentas at different stages of pregnancy was studied.
2. The oxygen consumption of the human placenta decreases gradually as pregnancy advances, a fact in keeping with the changing histologic picture of the organ.
3. The oxygen consumption of the term human placenta is not influenced by the use of analgesics or anesthetics during labor.
4. Addition of glucose into the phosphate Ringer's solution does not increase the oxygen consumption of the human term placenta.

C. O. MALAND.

Blanco, J. T.: Placental Neoplasms, Rev. de cir. 14: 299, 1943.

Placental neoplasms are reviewed and discussed, with a case report, by the author. Placental neoplasms may be of either maternal or ovular origin. Those of maternal origin develop from the decidual cells and are of the conjunctival type, do not produce an increase of prolactin, and are not necessarily the result of pregnancy. They are exceedingly rare and less malignant. Those of ovular origin arise in the epithelium, present a cellular polymorphism, characterized by anaplastic cells of Langhans, syncytium with monstrous deformities and at times with metaplasia of a decidual tendency and deformed decidual cells, of reactive significance and also with metaplastic tendencies that approximate morphologically those of the syncytium.

The diagnosis of these tumors is based on surgical exploration, histologic study and hormonal investigation. The prognosis is grave in the chorionepitheliomas, less serious for deciduomas, not serious in cases of benign mole and reserved in those of penetrating mole. The cases which are followed by spontaneous cure or after curettement are not true neoplasms, but simply retention of active placental rests or decidual endometritis. The only treatment is surgical removal, leaving radiation therapy for inoperable cases.

J. P. GREENHILL.

Jones, G. E. Seegar, Gey, G. O., and Gey, M. K.: Hormone Production by Placental Cells Maintained in Continuous Culture, Bull. Johns Hopkins Hosp. 72: 26, 1943.

It has been demonstrated that placental cells produce cyonin, that is, chorionic gonadotropin. The type of cells apparently responsible for this activity are the Langhans' cells. These cells will produce cyonin under conditions found in continuous tissue cultures and may retain this capacity as long as six months in culture. It has not been possible to demonstrate that placental cells can produce estrogen under similar circumstances.

C. O. MALAND.

Pregnancy; Physiology, Diagnosis

Salles, A. de Aquino: *The Frank Eight Hour Test for Pregnancy*, An. brasil. de ginec. 15: 467-476, 1943.

The author describes Robert Frank's eight-hour test for pregnancy which is based on the observation that chorionic gonadotropin produces a marked hyperemia of the ovaries in immature rats, detectable eight hours after the first injection. In 50 cases the results were so consistently satisfactory as to merit recommendation of this test which is simple, rapid and comparatively inexpensive.

J. P. GREENHILL.

Merchante, F. R.: *Contribution to Study of the Blood During Pregnancy*, Semana méd. 49: 1273, 1942.

Merchante studied the blood in 46 pregnant women. Hemoglobin was determined by the method of Wong, and cell volume by the method of Wintrobe. The red cell count also was determined. It was possible to follow eleven women from the first to the ninth month; the others were not followed regularly, through lack of interest or fear.

Results of the study show that the quantity of hemoglobin per cubic centimeter, the number of red cells per cubic millimeter and the cell volume are diminished from the beginning to the end of pregnancy. The level of hemoglobin shows a slight increase in the second month, but decreases abruptly in the third, and more slowly later, increasing in the eighth, and ascending slightly in the ninth month. The variation is from 12.55 grams per 100 cubic centimeters in the first month to 11.45 grams in the ninth, exceeding 13 grams in the second month.

The number of red cells per cubic millimeter decreases progressively from the beginning to the end of pregnancy, with at times a slight relative increase in the fourth month. The figures vary between 4,358,000 in the first month and 3,572,000 in the ninth. The cell volume descends progressively from 42.42 per cent in the first month to 38.96 per cent in the ninth, showing, in some instances, a slight increase in the second month.

J. P. GREENHILL.

Sloman, Lysbeth: *The Hippuric Acid Excretion Test in Pregnancy*, M. J. Australia 1: 293, 1943.

The author performed tests to establish figures for normal pregnancy and for complications of pregnancy without known liver disease. It was also determined how soon after parturition the hippuric acid excretion returns to normal. The figures for normal pregnancy indicate a progressive reduction in the excretion of hippuric acid as the pregnancy advances, while after parturition there is a statistically significant increase in the amount excreted, and the normal value for nonpregnant subjects is approached. The hippuric acid excretion rate for women up to three months pregnant is within the normal range for nonpregnant subjects, averaging 2.84 grams of benzoic acid. From 3 to 6 months there is a decrease in the excretion of hippuric acid (2.42 grams) and from 6 to 9 months there is still a further decrease (2.15 grams).

Of 22 patients with toxemia of pregnancy, the mean rate of excretion of benzoic acid was 1.96 grams. The author divides the toxemias into albuminuria, hypertension, hyperemesis, and pyelitis of pregnancy.

Tests were performed on 30 women whose hippuric acid excretion was tested before and after the baby was born. Results show that 18 of these patients reached or exceeded an excretion of 2,151 grams of benzoic acid on or about the eighth day of the puerperium. The majority of the patients suffering from

toxemia of pregnancy, however, failed to reach Quick's figure for normal excretion by about the tenth day of the puerperium. There is statistically a highly significant difference between the means of the tests carried out during the puerperium on toxemic patients and the tests carried out during the puerperium on normal patients. This was most marked in the pyelitis cases and in the opinion of the author was due to kidney dysfunction.

WILLIAM BERMAN.

Radiation

Wasson, W. Walter: Intravaginal Roentgen Irradiation of Cancer of the Cervix, Radiology 40: 454, 1943.

The author describes another method of intravaginal roentgen irradiation of the cervix. The apparatus consists of a cylinder and proctoscopic light. The apparatus containing the x-ray tube may then be brought into contact with the cylinder and then clamped into position. This treatment is always combined with external roentgen irradiation of the pelvis. The cylinder may be angled to direct the rays against the cervix or into the broad ligaments or into any portion of the pelvis. By this method the rays are limited to an area conforming to the diameter of the cylinder. The author feels that with this method the results as to permanent cures will be no better in the early cases than those of radium and external roentgen therapy. There will be, however, less necrosis of the cervix, and likewise less infection of the vagina when this technique is employed. It is also felt that better results should be obtained in the advanced cases of cancer of the cervix than by any of the other methods which have been at the command of the radiologist.

WILLIAM BERMAN.

Kaplan, Ira: Irradiation of the Spleen and Pituitary for Control of Pubertal Bleeding, J. A. M. A. 121: 1199, 1943.

The author reviews the literature on the subject of irradiation of the spleen and the pituitary for intractable gynecologic bleeding. It is felt that the effect on the ovaries is an indirect one. In menorrhagia at puberty, or just beyond this period, roentgen therapy to the spleen and to the pituitary can be safely administered without interfering with subsequent ability to bear children. Even though in some instances radiation must be administered directly to the ovaries, seldom is sterilization in young women permanent, and whereas ova in the later stages of their differentiation are readily destroyed by irradiation the primordial cells which will produce subsequent ova are not affected.

The pituitary is definitely related to the productive organs, and has been shown to have a pronounced influence on menstrual function. This treatment of the spleen and the pituitary offers a readily available and effective method of treating pubertal bleeding without direct irradiation of the ovaries.

WILLIAM BERMAN.

Vaginal Infections

Fuentes, C.: Preliminary Note on the Isolation and Identification of *Monilia albicans* in Cases of Vaginitis, With an Experimental Study, Rev. méd. cubana 53: 937, 1942.

The organism, *Monilia albicans* or *Mycotorula albicans* was studied by the author in experiments on 32 animals, including rabbits, white rats and Cuban rats. Renal and hepatic lesions were the principal result in animals in which the organism was injected into the veins. Attempts to produce experimental vaginitis in the animals studied, by local instillation, were unsuccessful.

Acetylamino-hydroxyphenylarsenic acid produced rapid disappearance of clinical symptoms. The author believes that this treatment has not been used previously in vaginitis due to *Monilia albicans*.

J. P. GREENHILL.

Taft, A. E.: Concerning the Nature of Intracellular Inclusions and Their Significance in Gynecology, West. J. Surg. 51: 342, 1943.

The relationship of intracellular and extracellular "inclusion bodies" to certain fungi and bacterial spores is discussed as pathogenic agents in the vagina. Inclusion bodies have been found in the squamous epithelium of the vagina following use of the vaginal tampon. It is suggested that protozoa, fungi and bacteria which are often present in the vagina as pathogens, may in their growth process pass through certain stages of which the inclusion body may represent one stage. An illustration is shown in which a protozoon appears as a lifeless granule in all respects similar to a virus or spore. Therefore, the inclusion body found in vaginal epithelium may illustrate just one part of the life cycle of pathogenic molds, bacteria or protozoa.

WILLIAM BICKERS.

Venereal Diseases

Lewis, Robert M.: Management of Gonorrhea in the Female, Am. J. Syph., Gonorr. & Ven. Dis. 27: 418, 1943.

In the matter of diagnosis, laboratory evidence consisting of positive cultures or perfectly typical spreads is conclusive evidence of infection. Such evidence is usually obtainable with relative ease in acute cases. A small number of chronic cases yield positive laboratory evidence. Negative spreads and cultures, even if frequently repeated, must never be accepted as sure evidence that there is no gonococcal infection. While laboratory evidence is an essential part of diagnosis, in many instances history alone justifies a diagnosis of gonococcal infection and indicates immediate treatment.

Sulfanilamide, the first drug of real value in treating gonococcal infections, probably cured less than 30 per cent of the patients to whom it was given. Sulfapyridine proved very effective, but was found to be too toxic and, like sulfanilamide, has been discarded. Treatment with sulfathiazole is spectacularly successful in about 85 to 90 per cent of women with gonorrhea. Sulfadiazine is still under trial. Pregnancy does not contraindicate treatment. The only cases which might constitute an exception are those in which there is obvious kidney impairment.

Pelvic abscesses and those of the Bartholin glands still require drainage. The late results of gonorrheal salpingitis, adherent retroversions, etc., require surgical treatment.

There is no exact end point at which it can be said that cure has been effected. Medical judgment combined with negative bacteriologic evidence must be depended upon.

In the matter of gonorrheal vaginitis of children, it is now believed that in such cases the gonococcal infection is ordinarily limited to the vaginal mucosa and portio vaginalis of the cervix. Accurate diagnosis must depend on positive cultures. Sulfonamide therapy is the accepted treatment.

C. O. MALAND.

Anesthesia, Analgesia

Diddle, Lieutenant A. W., M.C., U.S.N.R., and Hill, Lieutenant A. M., M.C., U.S.N.R.: Pulmonary Embolism During Continuous Caudal Anesthesia, West. J. Surg. 51: 427, 1943.

Maternal respiratory collapse, fetal distress, local infection, meningitis and other complications of continuous caudal anesthesia have been reported but this is

apparently the first case of fatal pulmonary embolism to appear. The patient was a healthy young woman, aged 22, who received adequate prenatal care including weekly antiluetic therapy for her syphilis which had been under treatment prior to this pregnancy. Labor was spontaneous at term and after 6½ hours of labor, a 15 gauge B-D spinal needle was inserted into the sacral hiatus and withdrawal of the plunger recovered no blood. A No. 4 ureteral catheter was passed through the needle to the third sacral vertebra and the needle withdrawn over the catheter. Forty c.c. of 1 per cent procaine were injected and prompt anesthesia extending to just below the umbilicus with relaxation of the anal sphincter promptly followed. Repeated injections were given about every 25 minutes and two doses of a sympathomimetic drug were given for a sharp drop in blood pressure. After 3 hours of anesthesia an attempt to deliver the baby by forceps from an R.O.T. position made it necessary to give a small amount of ether in order to apply the Kielland forceps. While under anesthesia the patient gasped once and ceased to breathe. She could not be revived and a stillborn fetus was delivered. At autopsy a large pulmonary infarct in the right upper lung lobe was found. Careful search of the brachial, femoral, uterine veins revealed no thrombi. Upon opening the sacral canal a soft blood clot was found and beneath it a thrombosed vessel. Complete pathologic study of the entire body failed to reveal any other possible source from which the pulmonary infarct could have come. Failure to obtain blood upon introduction of the needle is not conclusive evidence that the venous plexus has not been injured.

WILLIAM BICKERS.

Nicholls, A. B.: Analgesic and Anesthesia During Labor, *Obst. y ginec. Latino-Am.* 1: 426-430, 1943.

In 1938 the author began the use of intramuscular injections of sodium evipan for the relief of labor pains during the first stage. Recently he began the routine use of the drug intravenously during the second stage. As soon as the patient is asleep he delivers the baby with forceps. He believes sodium evipan does not interfere with uterine contractions but increases the period of expulsion. Hence the need for the use of forceps. In a series of 700 labor cases delivery was spontaneous in 207 and by means of forceps in 363. The anesthetics employed were evipan (162) chloroform (304) spinal (42) ether (16) Schleich's solution (3) emarcon (2). No anesthetic was used in 83 cases.

J. P. GREENHILL.

Cesarean Section

Stearns, Howard C.: Extraperitoneal Cesarean Section, *West. J. Surg.* 51: 468, 1943.

Evolution of the extraperitoneal cesarean section is briefly reviewed. To Waters goes credit for the operation employed by this author but he emphasizes that its principles were first laid down by Physick, von Ritgen, Thomas, Skene, Davis, and most important were the contributions of Latzko.

The transversalis fascia surrounds the abdominal cavity and where it enters the pelvis it becomes known as the fascia pelvica and fascia endopelvica. One lamina of the endopelvic fascia envelops the bladder and another the uterus. The important fact is that the peritoneal plica, both anterior and posterior, are firmly attached to this fascia and cannot be dissected from it by blunt dissection while the fascia laminae are relatively easy to dissect from both the bladder and the uterus. This point is the keystone of the extraperitoneal operation, for the dissection of the fascia from the posterior and left lateral wall of the bladder permits mobilization of the bladder away from the lower uterine segment and permits the elevation

of the uterine-vesical plica while it is still attached to the fascia, thus exposing the lower uterine segment. A series of drawings graphically illustrates the technique and anatomy.

The operation was done on 16 patients, 15 of whom were primiparas. All but three showed definite signs of infection and 3 potentially so. All were in labor, the shortest duration having been 24 hours and the longest 56 hours. All mothers recovered and two babies died, neither of the fetal deaths could be attributed to the operation. In 3 cases the bladder was inadvertently opened and in 7 the peritoneal cavity was opened accidentally, all were closed without difficulty. No case of peritonitis developed.

WILLIAM BICKERS.

De Rezende, J.: My Experiences With the Arciform Incision for Cesarean Section in Infected Cases, *Obst. y ginec. Latino-Am.* 1: 257-292, 1943.

The author is convinced of the superiority of the transperitoneal, cervical cesarean section and prefers the longitudinal arciform incision to the straight vertical or horizontal ones because it is parallel with the muscle fibers. He is of the opinion that the extraperitoneal operation causes useless and even injurious complications resulting in prolonged intervention, delay in delivery of the fetus, accidental opening of the peritoneal cavity in 50 per cent of the cases, cellulitis and other complications. Since 1936, the author has performed 66 cesarean sections using a modified Kerr technique. There were two maternal deaths in this series but 64 women were contaminated at the time of operation, that is they had fever and tachycardia and they had had numerous vaginal examinations. He uses ether now but formerly employed spinal anesthesia. He gave up spinal because of its risk. Among 10 patients treated locally with sulfanilamide, 8 presented serious symptoms of intolerance.

J. P. GREENHILL.

Gynecology

McKim, G. F., Smith, P. G., and Rush, T. W.: Dysuria and Nocturia in the Presence of Normal Urine in the Female, *J. A. M. A.* 123: 603, 1943.

The authors quote numerous causes of bladder complaints without pyuria, and stress the importance of careful and complete examination of the patient as a whole, and not just the urinary organs. The question of gynecologic disorders with bladder symptoms is of extreme importance. Great stress is laid upon the psychologic approach to the patient's symptoms, since many of these cases show functional bladder complaints which, to the patient, are quite real. Many times the symptoms due to the functional derangement are much greater than the pathologic picture would indicate. Such minor alterations as changing the brand of the patients cigarettes, their diet, or their cough medicine often bring about remarkable changes in the patient's symptoms. Some of the office procedures used in examining these patients and treating them are described.

WILLIAM BERMAN.

Araya, R.: Fundamental Conceptions of Ovarian Histophysiology, *Obst. y ginec. Latino-Am.* 1: 293-316, 1943.

The author maintains that in accordance with previous studies he believes (1) there is no chronologic relationship between ovulation and menstruation, (2) there is no correlation between the development of the Graafian follicle and the corpus luteum and the changes in the endometrium, (3) the endometrial changes are brought about by estrogen and progesterone. The author maintains that the Graafian follicle and the corpus luteum have no great influence in the production of the ovarian hormones.

The author studied 50 extirpated ovaries and found absolute predominance of all forms of atretic follicles over the few fresh follicles and corpora lutea. He found lipids in the ovarian stroma in all stages of development of the atretic follicles and at all times in the cycle and maintains that this is evidence of the continuity of ovarian secretion and coordination with several other ovarian constituents.

J. P. GREENHILL.

Machado, L. M., and Junqueira, M. A.: Angiomatosis of the Cervix, Obst. y ginec. Latino-Am. 1: 348-355, 1943.

The authors describe two cases of a new gynecologic pathologic condition which consists of diffuse angiomatosis developing along the fibromuscular connective tissue submucous layer of the portio vaginalis. The etiology is considered to be chronic cervicitis. Typically the cervix is spongy, very tender, enlarged and violet colored. Histologically, the tissue resembles a hemangioma. The predominating symptom is metrorrhagia following coitus or any trauma. The exact diagnosis can only be made by biopsy. The treatment consists of amputation of the cervix. The prognosis is good.

J. P. GREENHILL.

Lima, B.: Colpectomy for Genital Prolapse, Obst. y ginec. Latino-Am. 1: 452-465, 1943.

According to the author colpectomy is the most efficient way to treat genital prolapse. In old women the operation competes with vaginal hysterectomy. Partial colpectomy is easy to perform under local infiltration anesthesia, and total colpectomy may be indicated in cases of prolapse following hysterectomy. The results of colpectomy are excellent and the mortality and morbidity are low.

J. P. GREENHILL.

Labor, Management, Complications

Hennessey, James P.: Occipitoposterior Position, J. A. M. A. 123: 524, 1943.

The many theories of the cause of occipitoposterior presentation are referred to. The author's experience has shown that the narrower the anterior pelvis, the higher the percentage of posterior positions. The etiologic importance of deflection of the head depends a great deal on such pelvic asymmetry as disturbs the equality of pressure on the ends of the occipitosincipital lever. Weak labor pains are also a factor. Flabby abdominal muscles are also important. Posterior positions are likely to be a cause of difficult labor, owing to the fact that the head is usually extended when the difficulty is encountered. On an average it lasts from 2 to 4 hours longer in a primipara, and from one to two hours longer in a multipara. In the majority of cases rotation occurs spontaneously, but the majority of obstetricians have tried to correct this abnormality and thereby shorten the second stage of labor and spare their patients. The prominence of the ischial spines is of greatest importance in determining whether intervention is necessary.

The author prefers not to give the patient any sedation until the cervix is dilated to 3 or 3.5 cm. Operative interference depends upon whether or not the head is engaged. If the head is at the spines $1\frac{1}{2}$ to 2 hours is allowed for rotation; if it is below the spines about one hour is allowed. When manual rotation is used the author uses Schumann's modification of Pomeroy's technique, and if forceps are used the author prefers Bill's modification of the Scanzoni maneuver. The author uses the Kielland forceps infrequently. Cesarean section was used in 17 cases but the occipitoposterior position was not the sole indication.

WILLIAM BERMAN.

Guiroy, A. J., and Albertelli, J. F.: Regulation and Management of Delivery, Bol. soc. de obst. y ginec. de Buenos Aires 22: 23-45, 1943.

On the basis of a preliminary experience, from 1933 to 1937, with 866 cases, the authors describe the routine use of pituitrin administered intravenously in cesarean deliveries and dystocia, and in patients who have difficulty in expelling the placenta because of an atonic uterus. In the years 1938 to 1941, the proportion of patients treated with oxytocics varied from 4.75 to 5.71 per cent of the total number of deliveries. A very small number of these had spontaneous deliveries, a larger group (approximately one-third) had cesarean births, and the remainder required obstetric intervention.

The authors stress the following points in regard to the technique. The product used must be pure and must be diluted in a solution which allows administration of the exact quantity required and in a correct length of time. The effective dose is 2 to 5 units. The hormone preparation must be injected slowly. It should be used promptly, preferably immediately after the cord is severed.

The value of the procedure is proved by intact placentas and membranes, no untoward general reactions and retraction of the uterus with a minimal loss of blood. Frequently when the cervix must be repaired, prolapse of the lower uterine segment is observed, and thorough investigation must be carried out to avoid this in suturing the cervix.

The authors have employed pituitrin in the acceleration of delivery in hydramnios, twin births, uterine fibroids, inertia during the expulsive period and in a great number of other obstetric circumstances.

J. P. GREENHILL.

Newborn

Sakula, J.: An Outbreak of Gastroenteritis in the Newborn Infant, Lancet 245: 758, 1943.

Epidemic gastroenteritis in the newborn infant often carries a mortality of 80 to 90 per cent. In the central Middlesex County Hospital on Nov. 1, 1942, it was observed that 2 out of the 6 babies in the premature nursery had a gastroenteritis and they were sent to the children's ward in the main hospital. Within a few days more cases appeared both in the nursery and in the ward to which the infected babies had been sent. On the fourth day after onset of the epidemic, the first mortality occurred. Healthy children were immediately isolated as well as the ill ones. Of the 31 children who were in the hospital, 18 became infected and 15 died, a case mortality of 83 per cent. The course of the disease was typical, beginning suddenly with severe and protracted vomiting, weight loss, normal or only slight elevation of temperature, and within a day or two these symptoms were followed by a persistent diarrhea. The stool often had an orange color. Treatment was apparently of no value. Saline with glucose was helpful in maintaining hydration. The sulfonamides were found to be without effect.

Autopsies were performed on 13 of the patients. Conspicuous was the absence of intestinal pathology. Most striking was the marked vascular congestion of the liver, thymus, and adrenals. The author believes the disease is probably not primarily an intestinal one at all, rather it is a generalized toxic condition. Culture of the feces revealed no consistent bacteriologic findings.

Suggestions are made as to how to prevent and how to stop (when already established) these outbreaks of gastroenteritis. Most important is the feeding problem. In this outbreak all cases occurred in babies who were either entirely or partly bottle fed. Completely breast-fed babies did not become infected. It is apparent then that infection occurs by way of the formula. A nurse should be appointed for the preparation of infant feedings whose sole duty it is to prepare and serve those formulas. Cross infection from other babies is thus avoided.

WILLIAM BICKERS.

Page, Earnest W.: The Excretion Rates of Histidine in Pregnant and Nonpregnant Women, West. J. Surg. 51: 482, 1943.

Histidine is an essential amino acid making up about 2 per cent of most proteins in the human body. Since Voegle first suggested that it was excreted in large amounts in pregnancy and Kapeller-Adler suggested a method of qualitative analysis that made it a practical laboratory procedure, much interest has been elicited. Published opinions as to its specificity in the diagnosis of pregnancy are at wide variance. The author has shown that random specimens of urine from the same patient show wide variations in histidine content. Using a method analysis which is described in detail, it was found that the variations were so great that no conclusions could be drawn when urine specimens were taken at random. Consequently it was decided to study the histidine excretion rate of the patients at various stages of pregnancy and the normal and toxemic patient, also the nonpregnant individual. Quantitative analysis for histidine by the author's method before and after the ingestion of 1 gram of this amino acid was done on these patients. The highest excretion occurs between the third and eighth month of gestation, the rate falls during the 2 weeks before delivery. Excretion rate is much higher in the pregnant than in the nonpregnant woman.

WILLIAM BICKERS.

Swan, Charles, Tostevin, A. L., Moore, Brian, Mayo, Helen, and Black, G. H. Barham: Congenital Defects in Infants Following Infectious Diseases During Pregnancy, M. J. Australia 2: 20, 1943.

The authors report the results of 61 infants examined, 36 having been found to have congenital defects. The mothers of 49 infants had suffered during pregnancy from rubella, 4 had no knowledge of any exanthem during this time, 9 contracted morbilli during pregnancy, and 2 suffered from mumps. In the cases of rubella during pregnancy, 31 of the infants born subsequently exhibited congenital defects. The abnormalities included cataract, deaf mutism, heart disease, microcephaly, and mental retardation. With few exceptions all of the 31 mothers with congenitally defective children had contracted rubella within the first three months of pregnancy. Four cases of congenital cataract are described, in some instances associated with other defects. The mothers, in these cases, denied all knowledge of an exanthem during pregnancy. No congenitally defective babies were born subsequent to the occurrence of morbilli in pregnancy. One case is recorded of congenital corneal opacity following mumps during pregnancy. The operative procedure and postoperative follow-up are described.

WILLIAM BERMAN.

Calvo, J. A.: Concerning the Congenital Pigmented Spot or Mongolian Spot in Colombia, Obst. y ginec. Latino-Am. 1: 317-323, 1943.

The "congenital pigmented spot" also known as the "Mongolian Spot" or "blue sacral spot" is observed frequently among babies born to those with pure African blood or a mixture of it in Colombia. The spot is evident on the first day of birth and is almost a constant finding in the yellow and Mongol races. The spot is pyriform in shape and its lower border corresponds to the intergluteal furrow. Its color varies from green to gray-blue and its size is that of an adult's hand or even larger. Occasionally it is aberrant for it has been observed on the shoulders, back, neck and even on the limbs. Histologically, it is produced by special pigments deposited in the deep dermal cells called the Boelz cells.

The Mongolian spot has been regarded as an atavistic sign remaining from the Asiatic origin of the human race.

Among 350 babies born in the Bogotá Maternity, twenty-four had the characteristic "Mongolian spot" an incidence of 7 per cent. Among the remaining children without spots, 50 per cent had been born of a European mother or father and a Colombian white-skinned male.

J. P. GREENHILL.

Pregnancy, Physiology

Schaffer, B., and Ricci, Guido: Influence of Age on Primiparity: A Study of 1,688 Cases, Bol. soc. de obst. y ginec. de Buenos Aires 22: 47-66, 1943.

Difficulties and complications attending a first pregnancy and childbirth have generally been considered to increase with the age of the mother, and 18 to 23 has been accepted as the optimal time for bearing a first child. The unfavorable factors in older women are largely due to loss of elasticity of the birth canal and deficiency in motor function of the uterus. But great differences exist in individuals, due to constitutional, gynecologic, social and even racial factors.

In a series of 3,835 obstetrical cases at the Maternidad Martin, 44 per cent, or 1,688 were primiparas. Of the primiparas, 25 per cent were less than 20 years, 43 per cent were between 20 and 25, 23 per cent were between 25 and 30, 7 per cent were between 30 and 35, and 3 per cent were more than 35.

Toxic conditions of pregnancy were most frequent in mothers between 30 and 35 years. Above 35, there was a marked decrease in these manifestations. The explanation advanced by the authors for this fact, which is contrary to most previously published statements, is that the older primiparas, as a group, were from a higher cultural level and were aware of the dangers of pregnancy at their age, and hence had better prenatal care.

In the group from 30 to 35, 5 per cent had breech presentations; in those more than 35, this percentage was increased to 11 per cent. In the oldest group, there were also 2 per cent transverse presentations. It is suggested that perhaps the decreased elasticity of the uterine musculature and abdominal pressure might account for these abnormal presentations.

Premature rupture of the membranes occurred with a frequency directly related to the age of the primiparas. The duration of labor also increased with age. In the group aged 30 to 35, 14 per cent had labors of 15 to 20 hours; 11 per cent 20 to 25 hours; 10 per cent, 25 to 30 hours; 2 per cent, 30 to 35 hours; and 10 per cent, more than 35 hours. In those over 35, 13 per cent had labors lasting more than 35 hours.

The mortality for the entire group of primiparas was 0.35 per cent. In those 30 to 35 years of age, it was 1.72 per cent; there were no deaths among the primiparas more than 35 years. Fetal mortality was practically uniform among mothers under 30, increased sharply among the older primiparas. Nevertheless, most of the fetal deaths were not due to prolonged or difficult labors, but resulted from prematurity and fetal maceration.

J. P. GREENHILL.

Leon, J.: Cystic Corpus Luteum and Lutean Cysts of the Ovary in an Apparently Normal Pregnancy, Bol. soc. de obst. y ginec. de Buenos Aires 22: 99-122, 1943.

The author reports the case of a woman, aged 33, a para iii, who had had amenorrhea for a few weeks, and complained of pain in the lower quadrant, nausea and vomiting. Vaginal examination revealed a slight increase in the size of the uterus and an adnexal cystic tumor. The Friedman reaction was positive. The diagnosis of early pregnancy with appendicitis and an ovarian cyst was considered as well as that of a persistent corpus luteum because the latter is characterized

by an enlarged ovary, amenorrhea and an increase of gonadotropic hormones. Operation revealed only slight inflammation of the appendix, but marked change in one ovary.

The corpus luteum in the removed ovary presented macroscopically the structure of the corpus luteum of gestation, that is, of an intrauterine gestation, but there was also no doubt that the gland displayed abnormalities similar to those seen in patients with ectopic pregnancy in which the embryo has succumbed. The corpus luteum was large (30 by 20 mm.), several millimeters larger than that generally observed in a physiologic pregnancy. Recently, numerous studies have shown that the size of the corpus luteum is greatest during the first months of gestation. Section of the corpus luteum showed that its wall of yellowish color, was 2 to 4 mm. wide, and the remainder was a cavity containing fluid. Histologic study of the wall of the corpus luteum showed the typical yellow cells which persist throughout pregnancy, some more obscure than others, probably representing different phases of secretory activity, as occurs in other glands of internal secretion; there also might be the possibility that the more definitely colored cells were filled with calcium salts, since this calcification is characteristic in gestation. Microscopic examination also revealed numerous thecal cells, which arise from the internal theca and play their greatest role in the second to third month, occupying the periphery or the corpus luteum, in intimate contact with the elements of the theca externa and the blood vessels.

The ovary also contained a number of lutean cysts of variable size, with gelatinous contents. It is unusual to encounter a number of these cystic formations in an apparently normal pregnancy.

Quantitative investigation seven days after operation revealed a definite hyperprolauria (more than 16,000 Brindeau units per liter of urine). The author admits that the concentration of prolaur may have been increased after removal of the corpus luteum, but cites experiments which showed that progesterone inhibits gonadotropic activity. The evidence of increased secretion of prolaur was the only abnormal finding in this patient. The pregnancy proceeded to term, and reports received from the patient, who had moved away indicated that gestation and delivery were entirely normal.

J. P. GREENHILL.

Pregnancy, Complications

Braze, Major Alexander: Bicornate Uterus With Pregnancy in Each Horn,
J. A. M. A. 123: 474, 1943.

The author presents the embryologic aspects of bicornate uterus and quotes the reports of the same in the literature. Stress is laid on the complications chief, of which, are hemorrhage and incarceration of one of the horns during labor. He reports a case of a pregnancy in each horn which delivered spontaneously only to be followed in three months by a prolapse of the left horn of the uterus with incarceration. A laparotomy was done which substantiated this diagnosis and a hysterectomy was carried out. The patient recovered.

WILLIAM BERMAN.

Lavarello, A.: Diabetic Coma in Pregnancy, Bol. soc. de obst. y ginec. de Buenos Aires 22: 71-75, 1943.

The author reports a fatality in a patient who had not been recognized as diabetic previously. A few days before the onset of the coma, she was abnormally thirsty, later she had severe vomiting, and then lapsed into coma, but was not brought to the hospital until 19 hours later.

In discussing the problem of diabetes and pregnancy, the author remarks that it is possible and appears probable that regulation of diabetes from the beginning

to the end of pregnancy can prevent all complications both to the mother and child. Not only should the diabetes be well controlled, but care should be taken that the metabolism of hydrocarbons takes place normally every hour of the day and night. In this connection, protamine-zinc-insulin is of great value.

During pregnancy, especially during the second and third trimesters, sudden and definite variations in the severity of the diabetes may occur; these may require more or less insulin. If the situation is not controlled promptly, it may result in serious consequences to both mother and child. As a rule, during the second and third trimesters of pregnancy, the diabetic patient should be examined every week or ten days. During parturition, the most rigorous care should be exerted to prevent acidosis and hypoglycemia in the mother. All authors agree that acidosis is a very serious complication and its fulminating progress can result in grave consequences. Occurrence of dangerous hypoglycemia in the newborn infant apparently can be prevented by maintaining the insulin intake of the mother within reasonable limits, and controlling the insulin dosage with frequent blood sugar determinations.

Routine cesarean section in diabetic patients is unnecessary and this procedure should be resorted to only when the obstetric indications for it are the same as in a nondiabetic mother.

J. P. GREENHILL.

Lastra, E. T., Jakob, A., and Sang, H. W.: Placenta Accreta and Placenta Previa, Obst. y ginec. Latino-Am. 1: 324-347, 1943.

One of the greatest dangers to the parturient woman which still exists in spite of progress in obstetrics is hemorrhage and its consequence, shock. Placenta accreta is one of the rare causes of hemorrhage and shock. The authors observed two cases of this complication. In the first case the membranes ruptured at the sixth month and because of failure of dilatation of the cervix in spite of good pains, a vaginal cesarean section was done. Hemorrhage followed retention of the placenta. Attempts to remove the placenta proved futile because of abnormal adherence. A diagnosis of placenta accreta was made and a supravaginal hysterectomy was performed. This woman had previously had a curettement 12 days after labor.

The second case reported was one of placenta previa treated by cesarean section. A curettement had likewise previously been done in the puerperium because of hemorrhage in puerperium. The placenta could not be removed so the uterus was amputated.

J. P. GREENHILL.

Lascano, J. C., and Valenzuela, J. R.: Concerning the Medical Treatment of Eclampsia, Obst. y ginec. Latino-Am. 1: 399-412, 1943.

During the last three years, the maternal death rate among the cases of eclampsia in the Cordoba Maternity was 6.7 per cent and the fetal death rate was 40.7 per cent. Strict medical therapy was carried out in 64.4 per cent of the cases. Among the sedatives employed were morphine, luminal and magnesium sulfate either alone or combined with intravenous hypertonic glucose solution and subcutaneous insulin. The authors believe that it is better to use a combination of luminal and chloral in women who have convulsions in pregnancy and a combination of luminal and magnesium sulfate when the convulsions occur during labor.

J. P. GREENHILL.

Society Transaction

THE OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF JANUARY 12, 1944

The following program was presented:

How a Child-Caring Agency Places for Adoption. Miss Beatrice MacNally, Adoption Supervisor of the Children's Bureau of Philadelphia (by invitation).

Legal Pitfalls in Child Adoption. Mrs. Lillian L. Strauss, Attorney (by invitation).

Post-Partum Sterilization: A Generally Indefensible Procedure. Edward A. Schumann, M.D.

